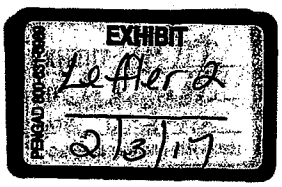
Exhibit A

ORIGINAL ARTICLE



MAYO CLINIC

Severe Spruelike Enteropathy Associated With Olmesartan

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Abstract

Objective: To report the response to discontinuation of olmesartan, an angiotensin II receptor antagonist commonly prescribed for treatment of hypertension, in patients with unexplained severe spruelike enteropathy.

Patients and Methods: All 22 patients included in this report were seen at Mayo Clinic in Rochester, Minnesota, between August 1, 2008, and August 1, 2011, for evaluation of unexplained chronic diarrhea and enteropathy while taking olmesartan. Celiac disease was ruled out in all cases. To be included in the study, the patients also had to have clinical improvement after suspension of olmesartan.

Results: The 22 patients (13 women) had a median age of 69.5 years (range, 47-81 years). Most patients were taking 40 mg/d of olmesartan (range, 10-40 mg/d). The clinical presentation was of chronic diarrhea and weight loss (median, 18 kg; range, 2.5-57 kg), which required hospitalization in 14 patients (64%). Intestinal biopsies showed both villous atrophy and variable degrees of mucosal inflammation in 15 patients, and marked subepithelial collagen deposition (collagenous sprue) in 7. Tissue transglutaminase antibodies were not detected. A gluten-free diet was not helpful. Collagenous or lymphocytic gastritis was documented in 7 patients, and microscopic colitis was documented in 5 patients. Clinical response, with a mean weight gain of 12.2 kg, was demonstrated in all cases. Histologic recovery or improvement of the duodenum after discontinuation of olmesartan was confirmed in all 18 patients who underwent follow-up biopsies.

Conclusion: Olmesartan may be associated with a severe form of spruelike enteropathy. Clinical response and histologic recovery are expected after suspension of the drug.

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Olmesartan is one of several angiotensin II receptor antagonists used for management of hypertension since 2002.[1] Diarrhea is a common adverse effect of many medications, although the mechanisms underlying diarrhea remain unclear in most cases. Enteropathy as a cause of drug-induced diarrhea has been reported previously with the use of azathioprine and mycophenolate mofetil.[2-4] We first suspected the possible connection between enteropathy and olmesartan when 2 consecutive patients referred to our institution for evaluation of presumed refractory celiac disease reported unexplained clinical improvement during hospitalization but prompt relapse following hospital discharge. They asked if the disease course could have been due to their hypertensive medications, which were withheld on hospitalization because of hypotension. At the same time, we were studying a cohort of patients with collagenous sprue and discovered olmesartan use in one-third of the patients with a recent diagnosis of the disorder.[5] As additional patients were identified with similar clinical features (eg, chronic diarrhea, weight loss, unexplained spruelike enteropathy with or without abnormal subepithelial collagen deposition, negative celiac serology, and lack of response to gluten exclusion), a perceived association between these features and olmesartan evolved. It also became clear that these patients were unlikely to have celiac disease, as all lacked IgA tissue transglutaminase antibodies and had never responded to a gluten-free diet. The clinical observation of improvement of gastrointestinal symptoms and subsequent demonstration of histologic recovery after olmesartan withdrawal prompted us to advise our patients with unexplained spruelike enteropathy to discontinue olmesartan. We reported our observation to US Food and Drug Administration officials and submitted reports using the MedWatch system.

In this article, we describe the clinical manifestations in 22 patients with unexplained spruelike enteropathy that improved clinically after discontinuation of olmesartan.

PATIENTS AND METHODS

This study was approved by the Mayo Clinic Institutional Review Board. Patients were considered for inclusion in the study if they had chronic diarrhea (>4 weeks) while taking olmesartan and met 2 additional criteria. First, the cause of their enteropathy

could not be established after a systematic diagnostic evaluation that included investigation for disorders associated with nonresponsive celiac disease as previously reported by our group.[6] Second, they had to improve clinically after discontinuation of olmesartan. Most of these patients had undergone extensive evaluation by their referring physicians and had had several therapeutic trials, without benefit. The electronic medical records of 24 such patients seen at Mayo Clinic in Rochester, Minnesota, between August 1, 2008, and August 1, 2011, were reviewed by one physician (M.L.H.). Two of the 24 patients were excluded from the study, 1 who had tropical sprue and 1 who improved clinically and histologically with oral budesonide before suspension of olmesartan.

Data Abstraction

Clinical and laboratory data were abstracted from the medical record. Only data that reflected conditions that existed before suspension of olmesartan were included as baseline data. We defined categories of body weight using body mass index and World Health Organization criteria.[7] Anemia was defined in women as a hemoglobin level of less than 12 g/dL (to convert to g/L, multiply by 10) and in men as a hemoglobin level of less than 13.5 g/dL. Hypoalbuminemia was defined as an albumin value lower than 3.5 g/dL (to convert to g/L, multiply by 10). HLA-DQ typing,[8] celiac disease serology (tissue transglutaminase antibodies or deamidated gliadin peptide antibodies by enzyme-linked immunosorbent assay and endomysial antibodies on monkey esophagus by indirect immunofluorescence),[9-11] and assessment of response to a gluten-free diet were investigated. Anti-enterocyte antibodies were tested using primate intestine by indirect immunofluorescence and were performed at The Children's Hospital of Philadelphia, as reported by Akram et al.[12] *Severe enteropathy* was defined by the presence of at least one of the following criteria: (1) need for hospitalization because of severe dehydration, electrolyte imbalance, and/or acute renal failure, (2) need for total parenteral nutrition, and (3) weight loss of more than 10 kg.

Histopathology

Pathology material (biopsy samples from the gastrointestinal tract) was reviewed by one of the authors (T.-T.W.). The number of intraepithelial lymphocytes per 100 epithelial cells, degree of villous atrophy graded with the modified Marsh classification,[13] presence of subepithelial collagen, degree of lamina propria inflammation, and presence of acute inflammation were assessed. The presence of aberrant or clonal intraepithelial lymphocytes was investigated by CD3 and CD8 immunostaining[14] and polymerase chain reaction,[15] respectively. When multiple small bowel biopsies were performed as part of the diagnostic evaluation and before withdrawal of the drug, the baseline biopsy was considered to be the small bowel biopsy performed closest to the date of suspension of olmesartan. Follow-up biopsies were defined as biopsies performed at least 30 days after the date of suspension of olmesartan. Other disorders of the gastrointestinal tract (when present) were diagnosed using accepted pathologic criteria (eg, microscopic colitis).[16]

Outcomes After Suspension of Olmesartan

Clinical response was defined as the resolution of diarrhea. Weight gain was considered a positive finding. *Remission* required both a clinical response and confirmation by normal findings on intestinal biopsy during follow-up. All patients who had been on a gluten-free diet were followed up after reintroduction of gluten and withdrawal of corticosteroids.

Medication Use

We reviewed the medication history of all patients, including the duration of treatment, dosage, and response of diarrhea to a trial of olmesartan withdrawal. Alternative antihypertensive drugs used after suspension of olmesartan are reported.

Statistical Analyses

Data were summarized using descriptive statistics, including total numbers and percentages for categorical variables and median or mean (range) for continuous variables.

RESULTS

The 22 patients (13 women) had a median age of 69.5 years (range, 47-81 years). Twenty-one of the patients were non-Hispanic white, and 1 patient was black. Patients were residents of 16 different US states (Table 1).

The most frequent clinical diagnoses at time of referral were nonresponsive/refractory celiac disease (n=10) and unexplained sprue (n=6). Most patients were taking 40 mg/d of olmesartan (range, 10-40 mg/d) for several months or years before the onset of diarrhea. Detailed information about the duration of exposure to olmesartan before onset of diarrhea was available in the medical record in 14 patients (64%). Among these, the mean duration was 3.1 years (range, 0.5-7 years). An additional 5 patients were taking olmesartan for at least 1 year before the onset of symptoms. Information about duration of exposure to olmesartan before onset of diarrhea was not available in 3 patients.

TABLE 1. Demographic Characteristics, Outcome, and Alternative Antihypertensive Drugs Used After Suspension of Olmesartan in 22 Patients With Sprue-like Enteropathy

Patient No./ sex/age (y)	Weight loss (kg)	Outcome after suspension of olmesartan[a]	Alternative antihypertensive drug
1/F/59	14	Remission	Metoprolol
2/F/62	11	Clinical response	None
3/F/72	31	Remission, weight gain (13.3 kg)	Bisoprostol-hydrochlorothiazide
4/M/66[b]	18	Remission, weight gain (11 kg)	Metoprolol
5/M/81	2.5	Remission, weight loss (4.1 kg)	Lisinopril, metoprolol
6/M/64	14	Clinical response	Amlodipine
7/F/65	11	Remission, weight gain (4.2 kg)	Amlodipine, hydrochlorothiazide
8/M/76	12	Remission, weight gain (13.4 kg)	Amlodipine, hydrochlorothiazide
9/M/64	20.5	Remission, weight gain (15.7 kg)	Amlodipine, hydrochlorothiazide
10/F/72	30	Remission, weight gain (28 kg)	Amlodipine, atenolol, hydrochlorothiazide
11/M/74	15	Clinical response	Hydrochlorothiazide
12/M/58	57	Remission, weight gain (23.4 kg)	Amlodipine, metoprolol
13/F/77	29	Remission, weight gain (9.7 kg)	Atenolol, hydrochlorothiazide
14/F/76	7	Remission, weight gain (2.9 kg)	Hydrochlorothiazide
15/M/68	18	Remission, weight gain (14.9 kg)	Metoprolol
16/F/71	9	Remission, weight gain (11.9 kg)	Triamterene, hydrochlorothiazide
17/F/66[b]	20.5	Clinical response, weight gain (13.4 kg)	Spironolactone, carvedilol
18/F/64[c]	50	Clinical response, weight gain (4 kg)	Amlodipine
19/F/75	41	Remission	None
20/M/47	32	Remission, weight gain (13.9 kg)	Metoprolol, amlodipine, doxazosin
21/F/71	18	Remission, weight gain (10.2 kg)	Atenolol, hydralazine
22/F/74	40	Remission, weight gain (6.3 kg)	None

[a]Weight change (defined by weight at diagnosis minus weight at last follow-up visit) is provided when available in the medical record.
[b]Case previously published.[5]
[c]Non-Hispanic black.

Clinical Manifestations

Diarrhea had been present for a median of 19.2 months (range, 3-53 months) before suspension of the drug. At the time of presentation, all patients had diarrhea and weight loss (median weight loss, 18 kg; range, 2.5-57 kg). Nausea and vomiting were present in 15 patients (68%), abdominal pain in 11 (50%), bloating in 9 (41%), and fatigue in 15 (68%). The onset of diarrhea was sudden in 9 patients. The stool frequency was extremely abnormal, with a median of 6 evacuations per day (range, 3-42 evacuations per day). Among 8 patients with timed stool collection, the mean stool weight was 933.1 g/24 h (range, 225-3225 g/24 h), and mean fecal fat was 28.3 g/24 h (range, 8-50 g/24 h). Although timed stool weight was not investigated in all patients, 14 patients (64%) required hospitalization because of severe dehydration (4 patients had acute renal failure). Total parenteral nutrition was necessary in 4 patients. At the time of the first visit at Mayo Clinic, 11 of the patients had normal weight, 6 were underweight, 4 were overweight, and 1 was obese. All but one patient (patient 16) met criteria for severe enteropathy.

Laboratory Findings

Results of IgA tissue transglutaminase antibody testing were negative in all patients. IgA endomysial antibody results were negative in all 9 patients who underwent testing. HLA-DQ typing was performed in 21 patients: DQ2 was present in 15 patients, DQ8 in 2 patients, and neither DQ2 nor DQ8 in 4 patients. Anti-enterocyte antibody testing was done in 19 patients (86%), and results were negative in 16 (including 7 patients who had a positive nonspecific nuclear pattern of unknown clinical significance) and positive with a linear/apical pattern in 3.

Fourteen patients (64%) had normocytic normochromic anemia (2 had elevated red blood cell distribution width suggesting anisocytosis); the lowest hemoglobin level was 9.3 g/dL. Ten patients (45%) had hypoalbuminemia; the lowest albumin

level was 2 g/dL. Twelve patients (55%) had one (n=3) or multiple (n=9) electrolyte abnormalities. Zinc deficiency was documented in 7 patients.

Small bowel bacterial overgrowth was confirmed by culture of duodenal aspirate ($>10^5$ colony-forming units per milliliter) in 12 patients at some point during clinical evolution. A trial of oral antibiotics was used in 10 patients without clinical benefit (rifaximin in 5, tetracycline in 3, ciprofloxacin in 1, and ciprofloxacin-metronidazole in 1). An additional 2 patients received no therapy for small bowel bacterial overgrowth.

Histologic Findings

In all patients, baseline intestinal biopsies demonstrated villous atrophy with variable degrees of mucosal inflammation (Table 2). Total villous atrophy was observed in 15 patients and partial villous atrophy in 7 patients. A thick band of subepithelial collagen deposition (collagenous sprue) was seen in 7 patients (2 cases had been reported previously[5]). Active/acute inflammation was observed in 15 patients, and increased intraepithelial lymphocytes were found in 14 patients. Aberrant (or clonal) intraepithelial lymphocytes were not detected among the 12 patients tested.

Colonoscopy with random colonic biopsies was performed in 13 patients (59%). Microscopic colitis was found in 5 patients (2 had lymphocytic colitis and 3 had collagenous colitis).

Biopsies of the stomach were available in 14 patients (64%). Lymphocytic gastritis was diagnosed in 5 patients and collagenous gastritis in 2 patients. Chronic gastritis was diagnosed in an additional 7 patients (1 had *Helicobacter pylori* infection).

Treatment and Subsequent Course

Most of the patients in our study had undergone several therapeutic trials, without apparent clinical benefit, before referral to Mayo Clinic, including the use of a gluten-free diet for months (n=20), systemic corticosteroids and/or budesonide (n=20), opioid-derived antidiarrheal agents (most often loperamide) (n=10), pancreatic enzymes (n=4), bile acid sequestrant (n=4), metronidazole (n=4), azathioprine (n=3), and octreotide (n=3).

Clinical response was observed in all 22 patients after suspension of olmesartan. Besides tapering of corticosteroids, no medication was needed to control diarrhea after clinical response was achieved with suspension of the drug. Patients following a gluten-free diet were advised to abandon the diet immediately if they lacked the celiac susceptibility genotypes or to gradually reintroduce gluten if they were HLA-DQ2 or DQ8 positive. No patient had recurrence of symptoms after restarting a gluten-containing diet. Follow-up body weight after suspension of olmesartan was available in 17 patients; 16 had weight gain, with a mean weight gain of 12.2 kg (range, 2.9-28 kg), and 1 patient (patient 5) who had edema at diagnosis lost 4.1 kg during follow-up despite clinical remission.

At the time of this report, follow-up intestinal biopsies have been performed in 18 patients (82%) after a mean of 242.3 days (range, 54-707 days) from the date of suspension of olmesartan. Histologic recovery of the duodenum was documented in 17 patients (Figure). Focal partial villous atrophy was observed in 1 case (patient 2) on a follow-up duodenal biopsy obtained 54 days after suspension of olmesartan. Follow-up gastric biopsies were performed at the same time as repeated biopsy of the duodenum in 6 of the 7 patients with either lymphocytic or collagenous gastritis (no gastric biopsy results were available for patient 11). Follow-up gastric biopsies showed normal mucosa in 4 patients and nonspecific mild chronic gastritis in 2 patients (patients 20 and 22). Follow-up colonoscopies with biopsies of the colon were not performed in the 5 patients with microscopic colitis.

DISCUSSION

We describe a group of patients with unexplained severe spruelike enteropathy while taking olmesartan. We also provide evidence of both clinical and histologic improvement after suspension of olmesartan. Celiac disease was excluded by conventional methods of serology and the absence of clinical response to a gluten-free diet.[17] Other less common enteropathies were excluded (Table 3).

We acknowledge that this case series lacks all the information necessary to prove causality but rather reflects an association. No deliberate rechallenge test with olmesartan was undertaken because of the life-threatening nature of the syndrome, although 2 patients reported anecdotally that their symptoms had worsened when they restarted olmesartan before the potential association was recognized, and 2 patients experienced improvement when olmesartan was stopped when they were hospitalized (for dehydration and hypotension) and worsened in the weeks following discharge and reintroduction of olmesartan. Resolution of the presenting symptoms and subsequent histologic improvement after suspension of olmesartan, in the absence of clinical evidence of other diseases associated with enteropathy, suggest that the association is not likely to be due to chance.

Pathologic findings in the duodenal biopsy can mimic celiac disease or collagenous sprue. Clinicopathologic correlation is advised to confirm the diagnosis of olmesartan-associated enteropathy. Pathologic evidence of involvement of other organs (eg, the

TABLE 2. Histologic Findings in 22 Patients With Olmesartan-Associated Enteropathy[a]

Patient No.	Baseline duodenal biopsy results: Villous atrophy	IELs (/100 epithelial cells)[b]	Acute/active inflammation	Thickened collagen band	Aberrant cells/clone[c]	Outcome follow-up duodenal biopsy results	Time d[d]	Other GI findings[e]: Gastric	Colorectal
1	Total	Normal	Yes	No	No/No	Normal	404	Lymphocytic gastritis (HP negative, immunostain)	Collagenous colitis
2	Total	80-100	Yes	Yes	No/NA	Improvement, focal partial villous atrophy	54	Chronic gastritis (HP negative, immunostain)	Normal
3	Total	Normal	Yes	No	No/No	Normal	231	NA	Collagenous colitis
4	Total	40	Yes	Yes	No/No	Normal	263	Collagenous gastritis	NA
5	Total	>100	Yes	No	NA/NA	Normal	54	NA	Normal
6	Partial	60	Yes	No	NA/NA	NA	NA	NA	NA
7	Partial	>100	No	No	No/No	Normal	159	NA	Normal
8	Total	40-60	Yes	No	NA/NA	Normal	143	Lymphocytic gastritis (HP negative, immunostain)	Normal
9	Total	60-80	Yes	No	No/No	Normal	188	NA	NA
10	Partial	Normal	No	No	No/No	Normal	404	NA	NA
11	Partial	50	Yes	No	No/No	NA	NA	Mild lymphocytic gastritis (HP negative, immunostain)	NA
12	Partial	Normal	Yes	No	No/No	Normal, focal active duodenitis	116	Mild active chronic gastritis (HP negative, immunostain)	Mild active chronic colitis
13	Total	40	Yes	Yes	NA/NA	Normal	171	Active chronic gastritis (HP negative, immunostain)	NA
14	Partial	60-80	No	No	NA/NA	Normal	240	Mild active chronic gastritis (HP negative, immunostain)	NA
15	Total	Normal	No	Yes	NA/NA	Normal	181	Mild chronic gastritis (HP negative, no immunostain)	Normal
16	Total	Normal	No	Yes	No/No	Normal	607	Collagenous gastritis	Collagenous colitis
17	Total	40-60	Yes	Yes	No/No	NA	NA	Mild chronic gastritis (HP negative, no immunostain)	Focal acute colitis
18	Partial	Normal	No (marked eosinophilia)	No	NA/NA	NA	NA	NA	NA
19	Total	30	Yes	No	NA/NA	Normal	76	Severe active chronic gastritis and ulceration (HP negative, immunostain)	NA
20	Total	Normal	No	Yes	No/No	Normal	702	Lymphocytic gastritis (HP positive)	Lymphocytic colitis
21	Total	80-100	Yes	No	NA/NA	Normal	179	NA	Lymphocytic colitis
22	Total	80	Yes	No	NA/NA	Normal	184	Lymphocytic gastritis (HP negative, immunostain)	Normal

[a] HP = Helicobacter pylori; IELs = intraepithelial lymphocytes; NA = not available.
[b] Normal, <25/100 epithelial cells.
[c] Aberrant cells defined by >50% CD3+/CD8- IELs on immunostaining; clone defined by T-cell receptor gene clonal rearrangement by polymerase chain reaction.
[d] Time from suspension of olmesartan to follow-up biopsy.
[e] Any time before suspension of olmesartan.

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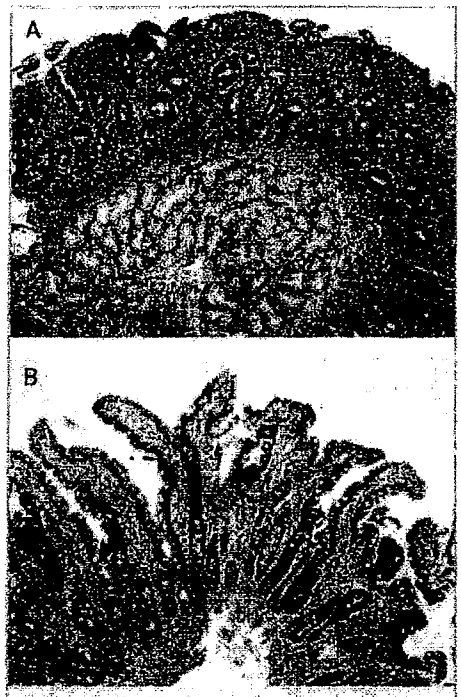

FIGURE. Photomicrographs showing reversible spruelike enteropathy associated with olmesartan (hematoxylin-eosin, original magnification ×100). A, Duodenal biopsy specimen obtained while the patient was taking olmesartan shows total villous atrophy and intraepithelial lymphocytosis. B, Biopsy specimen obtained 6 months after withdrawal of olmesartan and initiation of a gluten-containing diet shows recovery of villi on duodenal mucosa.

stomach and colon) suggests that this disorder may affect the entire gastrointestinal tract. We provide evidence of resolution of inflammation and/or fibrosis in the stomach and duodenum after suspension of olmesartan, implying that these changes are associated with the use of olmesartan. Even though follow-up colonoscopies were not performed in the 5 patients with documented microscopic colitis, clinical remission was achieved in all of these patients, a very unlikely outcome in the presence of persistent inflammation or fibrosis of the colon. Recovery of duodenal mucosa in a relatively short time (median of 8 months from suspension of olmesartan to follow-up biopsies) is a relevant clinical observation because mucosal recovery in other small bowel disorders, such as celiac disease, may take years to occur despite adherence to a gluten-free diet, especially in older adults.[18,19]

Finding small bowel bacterial overgrowth in 12 patients is intriguing and consistent with prior observations of association of small bowel bacterial overgrowth and enteropathy in symptomatic patients with celiac disease.[20,21] The reason for this association is unknown. Thus, although small bowel bacterial overgrowth is a well-recognized cause of chronic diarrhea in the right clinical setting,[22] in this series, the lack of clinical response to oral antibiotics suggests that gastrointestinal symptoms are not explained by the effects of an increased number of bacteria in the small bowel.

The mechanisms underlying olmesartan-associated enteropathy are unknown. The long delay between onset of olmesartan therapy and the development of diarrhea (and enteropathy) suggests cell-mediated immunity damage rather than type I hypersensitivity. Recently, angiotensin receptor blockers have been suggested to have inhibitory effects on transforming growth factor β action.[23,24] Transforming growth factor β is crucially important in the maintenance of gut immune homeostasis.[25,26] Olmesartan is an orally administrated prodrug (olmesartan medoxomil) that is rapidly metabolized to the active component (olmesartan) by esterases in the gastrointestinal mucosa, portal blood, and liver.[27] Nevertheless, the possible role of transforming growth factor β inhibition in olmesartan-associated enteropathy is a question that requires investigation. We do not know if other angiotensin II receptor blockers can be associated with a similar form of enteropathy, but active investigation for similar cases among patients using other drugs of the same class is under way. All our patients with olmesartan-associated enteropathy received antihypertensive drugs from a different class after suspension of olmesartan. HLA-DQ2 was present in 68% of patients with olmesartan-associated enteropathy, a prevalence higher than the 25% to 30% expected for the general population,[28,29] suggesting that perhaps

- Gastrointestinal symptoms (eg, chronic diarrhea, weight loss, steatorrhea)
- Negative IgA tissue transglutaminase antibodies (or endomysial antibodies)
- Evidence of enteropathy (villous atrophy) with or without collagen deposition or intraepithelial lymphocytosis
- Lack of clinical response to gluten exclusion
- Exclusion of other causes of enteropathy (eg, celiac disease)
- Evidence of clinical and histologic improvement after suspension of olmesartan

the presence of HLA-DQ2 may increase the risk of immune-mediated damage in these patients. This may be another example of drug-associated enteropathy of which the medical community should be aware and could result in the identification of several more cases.

CONCLUSION

We report a unique case series to support a novel association between severe sprue-like enteropathy and olmesartan. Physicians who encounter patients with diarrheal syndromes should consider medications as a cause, although the potential role for olmesartan had not been considered in these patients by any of the physicians prescribing the medications or treating the diarrheal illness.

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Exhibit B

UNITED STATES DISTRICT COURT

DISTRICT OF NEW JERSEY

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IN RE: BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION	*	CIVIL NO. 15-2606(RBK)(JS)
	*	JUDGE KUGLER
THIS DOCUMENT RELATES TO ALL CASES	*	MAG. JUDGE SCHNEIDER

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* PROTECTED INFORMATION *

DEPOSITION OF DANIEL A. LEFFLER, M.D.

ROBINS & KAPLAN

800 Boylston Street

Boston, Massachusetts

February 3, 2017 8:32 a.m.

Maryellen Coughlin, RPR/CRR

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deposition.

When we use the term olmesartan, you understand that to be the name of several marketed hypertension drugs which include Benicar, Benicar HCT, Azor and Tribenzor?

A. I do.

Q. And we may occasionally use the term ARB or ARBs, that's A-R-B-s.

You understand that's a class of Angiotension II Receptor Blockers that are used to treat hypertension?

A. I do.

(Whereupon, Deposition Exhibit 2, "Severe Spruelike Enteropathy Associated with Olmesartan," Rubio-Tapia, et al, was marked for identification.)

BY MR. CHRISTIAN

Q. We'll also be talking about a condition called sprue-like enteropathy, and I've marked as Exhibit No. 2 to your deposition an article that was published in 2012 in the Mayo Clinic Proceedings entitled, "Severe Spruelike Enteropathy Associated With Olmesartan." You're familiar with this article?

A. I am.

Q. And this was the first publication discussing the potential association between olmesartan and sprue-like enteropathy?

MS. SUTTON: Objection, form, foundation. You can answer.

A. Yes, so in -- this was the first article that really -- that really focussed on this.

The only other place that this showed up beforehand to my knowledge was in an article on collagenous sprue by the same authors of the Mayo Clinic, where they note that a number of patients were on olmesartan, and then this is the first article that followed that up.

Q. In the 2010 article that you referred to, they just list that some patients were taking olmesartan, correct?

A. Exactly.

MS. SUTTON: Objection, form. Just wait for me to finish.

Q. In that 2010 article you referred to, there's no discussion of a possible association between olmesartan and collagenous sprue or sprue-like enteropathy, correct?

MS. SUTTON: Same objection.

A. So in that article, they state that this is an association that deserves further evaluation.

Q. With respect to olmesartan?

A. With respect to olmesartan.

Q. And you understand that when I ask you questions today -- when I ask you questions about sprue-like enteropathy in patients taking olmesartan, that I'm asking you about the clinical features that are described in Exhibit No. 2?

MS. SUTTON: Objection, form.

A. So when I think about olmesartan enteropathy, it can cover a range of symptoms, many of which are noted in this paper but some that may not be.

(Whereupon, Deposition Exhibit 3, Table No. 3 from the Mayo 2012 article, was marked for identification.)

BY MR. CHRISTIAN

Q. Okay. Within Exhibit No. 2, there is a table number 3 on page 737. Just to make it easier to read I've marked a blowup, Exhibit No. 3, of that exact table.

You see here that this table is

describing the clinical features of sprue-like enteropathy associated with olmesartan?

A. Yes.

Q. And do you agree that these are the clinical features of sprue-like enteropathy?

MS. SUTTON: Objection, form, foundation.

A. So I think that these -- that many patients in many cases that I've seen with olmesartan enteropathy have these features, some or all of them.

I don't think this is a completely exhaustive list of all the features of olmesartan enteropathy, and I don't think that you need all these features to be present to have olmesartan enteropathy, but I think this is a representative table.

Q. And have you published a representative table of characteristics of sprue-like enteropathy with olmesartan?

A. I have not.

Q. But you have -- you have added additional clinical features that you consider to be associated with sprue-like enteropathy?

MS. SUTTON: Objection, form.

A. Based on subsequent reports in the literature and my own clinical experience, yes, I think that there are -- that it is acknowledged that there's a wider spectrum of presentation than was initially noted in this first 2012 article.

Q. And what features would you add to Exhibit No. 3 --

MS. SUTTON: Objection, form.

Q. -- that is not included by the authors of Exhibit No. 2?

MS. SUTTON: Objection, form. You can answer.

A. So I think that there are -- I think the way this table is, but it's not entirely clear what symptoms you need or what tests you need or don't need to diagnose olmesartan enteropathy.

I think gastrointestinal symptoms, as is sort of noted by the e.g., they don't suggest that the chronic diarrhea, weight loss and steatorrhea are the only symptoms you can have. The other ones that seem to be common are vomiting and abdominal pain.

At this point, you don't need a

negative tissue transglutaminase antibody to make the diagnosis of olmesartan enteropathy.

The enteropathy has been shown to be more variable and patchy, so it's not always -- you don't always see frank villous atrophy on every biopsy of a patient with olmesartan enteropathy.

The lack of clinical response to gluten exclusion I agree with. Again, the exclusion of other causes of enteropathy, I think as we -- as the clinical community has become more familiar with this condition, recognizes that once there is clinical improvement off of olmesartan you don't -- that you have by definition excluded other causes of enteropathy.

So I think the way this is written it suggests that you need to go through an exhaustive evaluation at the very onset before you consider the diagnosis, which I do not think is current standard of prac- -- of my practice certainly.

And, again, for clinical improvement after suspension of olmesartan, I certainly agree, but the histologic improvement, the need for a second invasive procedure would

not be considered routine.

Q. Dr. Leffler, is it your testimony that in order to diagnose sprue-like enteropathy you do not need to exclude other causes of enteropathy if the patient ceases olmesartan and recovers from their symptoms.

MS. SUTTON: Objection, form.

A. So I think the fact that your clinical syndrome improves with cessation of olmesartan does by definition exclude the other causes, 'cause no other cause of enteropathy, of malabsorption would be expected to improve when the only clinical change was the removal of the olmesartan.

Q. When I ask you questions today about sprue-like enteropathy -- well, let me strike that and rephrase.

You use the term "olmesartan enteropathy" in your report, correct?

A. Correct.

Q. And when I'm asking you questions about sprue-like enteropathy, you understand that that is the same thing as olmesartan enteropathy?

MS. SUTTON: Objection to form.

A. So I actually think of those terms

likely be doing blood work anyway. But, again, if the patient responds well to olmesartan withdrawal, there'd be no need to get that celiac blood test.

Q. Objection, non-responsive.

Dr. Leffler, is it your opinion that to diagnose sprue-like enteropathy associated with olmesartan that you do not need a negative IgA test?

MS. SUTTON: Objection, form, asked and answered.

A. So, yes, I think that you do not need a negative IgA-tTG celiac blood test, tissue transglutaminase test, to diagnose olmesartan enteropathy in all cases.

Q. Well, do you need it in some cases?

A. I think that because of the -- often the difficulty and the lack of awareness of olmesartan enteropathy, many patients are initially considered to have celiac disease and placed on a gluten-free diet, whereas they do not have response to a gluten-free diet, but in those cases, confirming that they do not have celiac disease, which is the reason they're not responding to a gluten-free diet, by having a

negative tTG at time of that initial consideration of celiac disease can be helpful. But, again, the diagnosis is based on the response to olmesartan withdrawal, not the results of the celiac blood test.

Q. Doctor, you understand and agree that celiac disease is something different than sprue-like enteropathy associated with olmesartan?

A. Yes, these are different conditions.

Q. And you agree that olmesartan does not cause celiac disease, correct?

A. So olmesartan does not cause -- we do not believe causes celiac disease.

There have been some cases reported where patients after having olmesartan -- what appears to be olmesartan enteropathy are then later found to also have celiac disease. Whether or not an initial injury to the small intestine causing increased passage of antigens, such as gluten, could in some cases trigger celiac disease in an otherwise genetically predisposed individual I think is an open question. It's plausible. We see that with other conditions.

independent clinical condition was in the 2012 article.

Q. So the first time that you became aware of a clinical condition called severe sprue-like enteropathy associated with olmesartan was when Exhibit No. 2 came out, was published?

MS. SUTTON: Objection, form and foundation.

A. Yes, I think it was after this 2012 article that I and many of my colleagues became convinced that this was a true clinical entity.

Q. And you recognize that the authors of Exhibit No. 2 when they published this, recognized this as a novel association between sprue-like enteropathy and olmesartan, correct?

MS. SUTTON: Objection to form.

A. Correct. Aside from this publication in 2010 noting that there was, I am not aware, and I do not believe they were aware of any prior publications in the medical literature.

Q. I'm going to mark as Exhibit No. 4 to your deposition a 2010 publication entitled "Gluten-Free Diet and Steroid Treatment Are Effective Therapy for Most Patients With

Q. And the symptoms that you list here, one of the sources of those is Exhibit No. 2, the 2012 publication, correct?

MS. SUTTON: Objection, form.

A. Correct, one of the -- yeah, correct.

Q. And you include things that they included in their Table 3, including diarrhea and weight loss, correct?

A. Correct.

MS. SUTTON: Objection, form.

Q. When you say "related symptoms," are there other symptoms that you include as characteristics of sprue-like enteropathy?

A. So yes. I mean -- so there are -- you know, when people have gastrointestinal injury from sprue-like enteropathy or from similar conditions like celiac disease, there can be a pretty wide range of symptoms, anything from alternating bowel habits. So patients don't always have diarrhea. They can even have periods of constipation. They can have fecal incontinence, severe fatigue. There can be extra intestinal manifestations, skin changes related to vitamin deficiencies, bone loss. So, you

know, the related symptoms, especially around malabsorption and around severe gastrointestinal injury, can be fairly broad.

Q. If someone wanted to know what Dr. Leffler's characteristics of sprue-like enteropathy are, where would they go to find that?

MS. SUTTON: Objection, form.

A. So outside of a gastroenterology board review textbook that I've written where I did write about olmesartan enteropathy, there really -- there's nowhere where I have a specific list of symptoms that I would associate myself with -- that I've written where I've associated with olmesartan enteropathy. I think what I and most clinicians would do is read through the literature and read through the many case reports and case series, as well as taking into account our own clinical practice, to develop an idea of what the spectrum of symptoms that you see associated with olmesartan enteropathy are.

Q. So this test preparation guideline that you prepared; is that what you're referring to?

A. Yes.

MS. SUTTON: Objection, form.

A. Yeah, as we talked about a few minutes ago, there is no specific symptom that is specific to a specific etiology of intestinal damage. So you damage your intestine, whether it's due to a virus or celiac disease or olmesartan, and you can have very similar symptoms.

Q. Is there a number of symptoms that would be required before you could diagnose somebody with sprue-like enteropathy?

A. No, not at all. Just like with celiac disease, some people can be relatively minimally symptomatic. You know, we -- actually, probably even with celiac disease people can be totally asymptomatic despite having significant intestinal damage leading to extraintestinal manifestations like liver damage or bone loss. So you don't need symptoms. There's no symptom threshold to make a diagnosis for any gastrointestinal disorder.

Q. So if you have a patient come in to you, Dr. Leffler, that was taking olmesartan, had experienced weight loss. They took -- you took them off olmesartan and they gained weight back,

history and all you know is somebody has abdominal pain it would be very hard then to know what could be the potential cause of that symptom.

Q. You noticed when you were looking at the medical literature on sprue-like enteropathy that there is a wide variation of what may be termed latency -- I mean onset of sprue-like enteropathy symptoms from the time that the patient began olmesartan, correct?

A. Correct.

Q. Okay. That ranges anywhere from a matter of a few weeks after a patient starts taking olmesartan, correct?

A. Correct.

Q. Up to several years, correct?

A. Correct.

Q. You excluded in your MedWatch review a patient who had only been on olmesartan for one week before symptoms began.

Do you have a threshold where you would exclude patients as not having sprue-like enteropathy based upon a shorter duration of usage?

MS. SUTTON: Objection, form.

A. So I specifically do not have an absolute threshold. I do think though, you know, because the majority of cases described of olmesartan enteropathy had been on for months or years, a case that occurs that quickly is perhaps more likely to be a different mechanism of adverse drug reaction or hypersensitivity reaction or the like.

So, again, while this case, if there was more data, may wind up having been completely consistent with olmesartan enteropathy, it was atypical in that way, and so just in order to have a -- yeah.

Q. And is there any time -- so you're not ruling out any duration of time between olmesartan usage and onset of symptoms that you would exclude as being too short of a time for someone who has sprue-like enteropathy, correct?

MS. SUTTON: Objection, form, asked and answered.

A. So I think that an immune reaction like this needs to develop. It shouldn't happen on the first exposure.

So if you took -- if you had the symptom with your first exposure, your first pill

of olmesartan, I would think that that could not be -- that would not be consistent with what we understand to be the mechanism of olmesartan enteropathy.

After that, though, it's just like in celiac disease, you see people develop it very quickly, in infancy, and you see people in their, you know, late 60s, 70s, 80s even develop celiac disease for the first time. So I think outside -- but they have to have some time of initial exposure in order to develop the disease.

Q. Do we know why there's such a broad range in latency in celiac disease?

A. We have some ideas. You know, there is likely a -- you know, you have the genetic predisposition for celiac disease, which you have since birth, obviously, 'cause it's genetic. Then you have the one other necessary component which is gluten exposure. So, obviously, you can't get celiac disease until you have exposure to the antigen, same as with olmesartan enteropathy, and then there are a number of other environmental and genetic factors which play a role in peoples' predisposition to get celiac disease. And so for some people who

are in the right environment and have the right set of complementary genes, they are highly likely to get celiac disease, and it takes very little so they get it very quickly. Other people have a higher threshold, and it probably takes a second environmental hit at least. That's why we see people develop celiac disease after pregnancy, after a gastrointestinal infection, after a surgery, after chemotherapy. You need a second stressor to damage the intestine or stimulate the immune system such that it can respond to gluten in an improper way.

Q. And is it your opinion that for sprue-like enteropathy you need a second stressor to have that come into fruition?

MS. SUTTON: Objection, form.

A. So I think this is likely very similar to celiac disease. Whereas in some people based on the -- maybe the microbion, maybe their environment, maybe their pre-existing genetics, you probably don't need a second hit. They're probably predisposed from the very beginning, and other people you likely do need some extra event in order to precipitate that immune reaction, and that's why you see that wide

range of latency in these types of diseases.

Q. And you've seen in sprue-like enteropathy patients who were on olmesartan for a number of years, correct, before exhibiting symptoms of sprue-like enteropathy?

MS. SUTTON: Objection, form.

A. Correct.

Q. And is there any cutoff that you would impose? If someone was taking olmesartan for ten years and began having symptoms, you would still be able to diagnose that person with sprue-like enteropathy?

A. Yes, using celiac disease as the analogy. I think as long as there's continued exposure to the drug, there is no -- there's no time at which it is not possible to develop that.

Q. Do you think it's unusual for a distinct clinical entity to have such a broad range of latency?

MS. SUTTON: Objection, form.

A. You know, because of our -- because of what we know about celiac disease, and actually all -- and most other inflammatory disorders, especially in the gastrointestinal tract. You know, think of Crohn's disease. You

know, there's two peaks, one in the teens and early adulthood and the other in the 40s and 50s. Same disease, but it's just a hugely different latency, decades different. But we think it -- you know, for Crohn's disease we think it's both an improper reaction to the intestinal microbion which you've had with you your entire life. So I think this is just what we see with these type of diseases, that latency varies based, again, on genetics and environment and a variety of other factors.

Q. Going to the topic of dechallenge. So you're talking about after someone has some symptoms of sprue-like enteropathy. They're on olmesartan, and you take them off olmesartan, that would be what we refer to as dechallenge?

A. Correct.

Q. In order for there to be a positive dechallenge, you would require clinical resolution of the symptoms after olmesartan withdrawal?

MS. SUTTON: Objection, form.

A. So I would say you would need at least clinical improvement. Resolution, as we see with, again, celiac disease can take a long

time, and so, you know, months. In some patients, especially if they're older patients with comorbidities, we know from celiac disease that it can take over a year to really get a clear clinical -- you know, even that it may never get full clinical resolution, but they'll get improvement, but it often takes months. So as long as there's improvement, I would consider that a positive dechallenge.

Q. So would you disagree with the authors of the Mayo Clinic study that a dechallenge requires clinical resolution of the symptoms after olmesartan withdrawal?

MS. SUTTON: Objection, form, foundation.

A. So I think that if -- yeah, I think -- I mean -- can I see that? Where do they say that, do you know?

Q. Sure.

(Whereupon, Deposition Exhibit 5, "Sprue-Like Enteropathy Associated With Olmesartan: A New Kid on the Enteropathy Block," Hujoel, et al, was marked for identification.)

BY MR. CHRISTIAN

Q. I've marked as Exhibit No. 5 a study by Hujoel and Rubio-Tapia from 2016 entitled "Sprue-Like Enteropathy Associated With Olmesartan: A New Kid on the Enteropathy Block." Have you reviewed Exhibit 5 before?

A. Yes, I have seen this paper before.

Q. And do you see on the first column the last full sentence of Exhibit 5 says, "Confirmation of diagnosis requires a clinical resolution of symptoms after olmesartan withdrawal." And you're telling us that you disagree with that?

MS. SUTTON: Objection to form.

A. So I think that I would actually agree more with their figure on the -- Figure 1 on page 63 where they have Step 1 is olmesartan withdrawal, and then they use the term response rather than resolution, 'cause I think that's really what we expect to see.

Q. So you do disagree that confirmation of diagnosis requires clinical resolution of symptoms after olmesartan withdrawal?

MS. SUTTON: Objection to form.

A. Yes, I think full resolution is not necessary but response is, as they say later in Figure 1.

Q. And their Figure 1 is their outline of a diagnostic chart for sprue-like enteropathy?

A. Yes, correct.

Q. And you see the "Supporting evidence" --

A. Mm-hmm.

Q. -- over on the right-hand side. "Patient taking olmesartan," correct?

A. Correct.

Q. "Confirmation of small bowel histology findings consistent with villous atrophy and/or collagenous sprue." Now, you disagree with that requirement, correct?

MS. SUTTON: Objection form.

A. So in this algorithm, they actually start with seronegative villous atrophy. So they start with the knowledge that the patient has enteropathy.

If they started with the suspicion based on clinical symptoms, then I would disagree, but since they already have this -- you know, that invasive procedure has already been

done. So once it's done, yes, you would look to confirm that with the biopsies 'cause there's no added risk to the patient.

Q. But what level of improvement would qualify as a positive dechallenge in your opinion if not complete clinical resolution?

A. Yes, so improvement varies from -- improvement really is -- it's hard to make a single rule for how much improvement you need 'cause the clinical presentation can be so different.

You know, in somebody who has severe malabsorption and weight loss and being hospitalized for dehydration, you know, improving to the point that they no longer need to be hospitalized and their weight is stable, even they have some ongoing diarrhea, is a substantial clinical improvement.

In somebody whose symptom is only, you know, more moderate, you know, diarrhea, occasional vomiting, you know, they would actually get much better. They would have to be, compared to that first person, much better to actually see a clinical improvement.

So really it depends on what they

start with. And it's hard to define a single clinical threshold across the entire population for what clinical -- for what improvement is.

But, again, talking -- I mean, but it's not subtle when working with patients. They feel better. They know they feel better. If they were in the hospital and they're not in the hospital anymore. If they were going to the bathroom five times a day and now they might be going to the bathroom two times a day.

Q. So whether or not a patient qualifies under your opinion for a positive dechallenge, that's a subjective opinion?

MS. SUTTON: Objection, form.

A. I think it requires clinical evaluation of the patient in each case to understand whether they have had a clinical -- had a clinical improvement.

Q. And you would be the one to determine whether or not that improvement is sufficient enough to be considered a positive dechallenge, off of olmesartan, correct?

A. I think the patient's treating physician is in a good position to make that assessment.

Q. Okay. Do you know how many patients the Mayo doctors excluded from their cohort, from Exhibit No. 2, because they did not improve clinically after cessation of olmesartan?

A. I do not know that.

Q. Okay. Do you have a time period in which a patient after withdrawing from olmesartan would have to show some type of improvement for you to consider it a positive dechallenge?

MS. SUTTON: Objection, form.

A. So it was talked about a little bit already, but the time to improvement can be variable.

Unfortunately, it would be wonderful for patients if they always responded very quickly, but they don't.

And, again, the same in celiac disease, some patients, especially young or otherwise health patients, will respond quickly, in a matter of days or weeks.

Older patients, it takes longer to heal from anything as you get older, and that's the same with small intestinal injury.

So, you know, while you would expect in the majority of cases to see some

response within the first few months, maybe even weeks, in some cases it can reasonably take longer, and I don't think you can exclude olmesartan enteropathy after a certain number of weeks or months if there's not been a substantial clinical improvement. In some cases, it's just going to take longer.

Q. So you can't, as you sit here today, exclude a patient who saw no improvement or symptoms a year after they stopped taking olmesartan? You can't say that that's not a positive dechallenge?

MS. SUTTON: Objection, form.

A. So I think without knowing the details of the case that it would be hard to comment on that. It really depends on what other evaluation has been done, what other causes have been considered.

Q. Are you willing to concede that if someone is taken off olmesartan and has no improvement over ten years that that would not be a positive dechallenge, or is that still open in your clinical mind?

MS. SUTTON: Objection to form.

A. You know, I think that has not been

described to date. I have not seen a case where there has been no improvement after years of -- years of treatment.

Whether there is a condition analogous to refractory celiac disease, where there is no improvement despite a gluten-free diet even though we know they have celiac disease. Whether -- because what we believe with refractory sort of diseases, after the immune system has been activated in the intestine for a number of years that becomes autonomous to some extent, and likely, because of the breakdown in the tight junctions of the intestine, you get influx of other antigens which lead to a more broad immune response such that you -- removing gluten is one part of therapy, but you also need steroids or other immunosuppressants to treat the disease. You know, that's a clear entity in celiac disease. Whether there is an analogous condition in olmesartan enteropathy, I have not seen. There might be out there. But, again, I think for the majority of patients you do see improvement within -- within months to even over a year, although it can be slow and partial.

Q. And, in fact, you would leave open

pathognomonic -- is that how you say it?

A. Pathognomonic.

Q. -- pathognomonic criteria to diagnose olmesartan enteropathy, correct?

A. That is correct.

Q. There's no unique clinical endoscopic criteria for sprue-like enteropathy?

MS. SUTTON: Objection, form.

A. That is correct.

Q. Your opinion is that it's currently made based upon the presence of typical GI symptoms and signs of malabsorption in patients taking olmesartan, correct?

MS. SUTTON: Objection to form.

A. That is correct.

Q. And the most common symptoms seen are diarrhea and weight loss?

A. You know, I think those are -- those are common symptoms seen. You know, I don't know that we actually have a full enough understanding of the spectrum of the condition to know what are the most common. Abdominal pain is also quite common. Vomiting is common. So I think they're all common. In terms of ranking, I don't know that we could specify which one is

more common and exactly percentages across the patient population.

Q. Are any of the symptoms necessary in your opinion to diagnose someone with sprue-like enteropathy?

MS. SUTTON: Objection, form.

A. So enteropathy just refers to damage to the intestine, and just like there are -- there's asymptomatic celiac disease and we still know it's celiac disease, if you were to do an endoscopy for an unrelated reason on someone with olmesartan, say they had reflux, you're looking for heartburn and esophagitis, and you found enteropathy, and then you took them off the olmesartan and that enteropathy resolved, that would be olmesartan enteropathy even in the absence of any symptoms. So I don't think there's any symptom specifically that's necessary for the condition.

Q. So you would be comfortable diagnosing someone with sprue-like enteropathy who had never had diarrhea symptoms?

MS. SUTTON: Objection, form.

A. Yes, you would -- in that case, again because you don't have a symptomatic

that a small intestine biopsy is not necessary to diagnose someone with sprue-like enteropathy; is that correct?

A. That is correct.

Q. Is that -- doing a biopsy, is that the only way to know whether or not a person has villous atrophy?

A. So the only way to confirm villous atrophy is through -- well, let me clarify that. That is the most common way to know that somebody has villous atrophy, is through endoscopy with biopsy, and that would be the majority of cases. You can also do other tests.

The other one would be -- the other one that is used sometimes in some cases is videocapsule endoscopy, the pill camera, where you can see classic changes of scalloping in the intestine associated with villous atrophy without doing an endoscopy biopsy.

Q. You can't diagnose villous atrophy just by some symptoms, correct?

A. That is correct. You can suspect a malabsorptive condition due to villous atrophy, but you could not document that.

Q. And you say in your report that a

biopsy is needed to confirm response to withdrawal of olmesartan, correct?

MS. SUTTON: Objection, form.

A. Let me look at my report where I said that.

Q. Sure. If you'd look at Paragraph 11 of Exhibit No. 1.

Do you see the second sentence down you say, "However, biopsy can be helpful in ruling out other disorders" --

A. Yeah.

Q. -- "or to confirm response to withdrawal of olmesartan," correct?

A. Correct, and I -- yes, so I agree with that. So biopsy can be helpful, and it is not necessary, but it can be helpful in ruling out other disorders or confirm response withdrawal, especially if the clinical criteria are not so clear and if there has not been -- if the symptoms are milder or the response, symptomatic response, is not clear, a biopsy can be helpful.

Q. You consider olmesartan enteropathy to be a cause of villous atrophy, correct?

A. I do, correct.

the new drug application for Benicar, correct?

A. I did not.

Q. Do you know if there's any scientific evidence of enteropathy in animals receiving high doses of olmesartan?

A. I have not seen evidence of that.

Q. And you I think recently this week reviewed some of the expert reports from Daiichi-Sankyo's experts?

A. Yes, I did.

Q. Do you know Dr. Keith Wilson?

A. I do not.

Q. Do you know Dr. Gerald Turner?

A. Gerald Turner from -- the pathologist from -- initially from the University of Chicago and now at Brigham & Women's Hospital?

Q. Yes.

A. Yes, I do.

Q. Have you collaborated and worked with Dr. Turner?

A. We have not had actual scientific collaborations, although we've had discussions.

Q. Do you have an understanding that he has a good reputation in the community as a pathologist?

Q. And you have not published on the proposed mechanism of action for how olmesartan could cause sprue-like enteropathy, correct?

A. I have not.

Q. You're relying upon the published literature by others; is that correct?

A. That is correct and upon analogy to my knowledge and writings on celiac disease, immunology and pathophysiology.

Q. You list, Dr. Randall Tackett's expert report. Is that something that you reviewed.

A. Yes.

Q. In his report he says that the peer-reviewed literature has elucidated the plausible biological mechanism by which olmesartan causes enteropathy.

Do you agree with that statement?

A. Could I see the report?

Q. Yes. Did you bring your reliance materials with you here today?

A. I did.

Q. I don't know if you have that report while we're looking.

A. Let's see. I should somewhere.

exhibits, they were all published in 2015; is that correct. Actually, one of them is 2016, I think. No, 2015.

MS. SUTTON: Objection, form.

Q. Well, can you confirm, Dr. Leffler, that Exhibits 17, 18, 19 and 20 were all published in 2015?

A. Correct.

Q. And there's nothing that -- no published peer-reviewed literature on the proposed mechanism of action that you rely upon that was published before 2015, correct?

MS. SUTTON: Objection, form, misstates testimony.

A. Yeah, these are the articles I relied on for -- in the published literature for my opinion.

Q. And when you go through your opinions, you discuss several different elements that were examined in these papers including in the Marietta paper, which is Exhibit 17, correct?

A. That's correct.

Q. And in this paper, Exhibit 17, one of the things they looked at was IL-15, correct?

A. That's correct.

Q. And they also looked at CD8, CD4, FoxP3, granzyme B and psmad 2/3, am I correct about that?

A. Yes, that is correct.

Q. And you discussed the fact that CD8 and granzyme B cells are the main mediators of damage to intestinal epithelium, correct?

A. That is correct.

Q. Okay. And the epithelium is the surface of the intestine?

A. The surface, the lining.

MS. SUTTON: Wait for him to finish his question. It makes it hard on the court reporter.

A. Yes, that is correct.

Q. Okay. And when we look at the results of the Marietta paper, Exhibit 17, we find that the CD8 cells -- they did find increased number of CD8 cells as you acknowledge, correct?

A. That is correct.

Q. And you added in your report profound increase, I think, correct?

MS. SUTTON: Objection, form.

Q. Paragraph 27.

A. Yes. Profound increases, yes, correct.

Q. The authors of that study only distinguished there's an increase, correct?

A. Correct.

Q. The CD4 cells that they looked at -- when in celiac disease, you see an increase in CD4 cells, correct?

A. That is correct.

Q. So one difference that we see between these two entities in Exhibit 17 is that there was no increase in CD4 cells in the olmesartan patients, correct?

MS. SUTTON: Objection, form.

A. Yes, that is correct. You know, the CD4 cells and CD8 cells have different functions.

The CD8 cells -- the other name for those are cytotoxic, CT cells. So they're responsible for damaging the basically cells, for attacking other cells.

CD4 cells are helper T cells which are responsible for encouraging these cells to produce antibodies. And so that -- which is a plausible explanation for why in celiac disease

you see autoantibodies, to gluten, to Ttg, to DGP, but autoantibodies have not been seen in general in the olmesartan cases.

Q. So that's one difference between celiac disease and olmesartan sprue-like enteropathy?

A. It is.

Q. And then when they look at the granzyme B positive cells, there was not a statistically significant increase in the granzyme B positive cells, correct? You see that on Figure 2.

A. That is correct, there was a numerical increase, but it did not reach statistical significance.

Q. Okay. And in your report, you did not include that fact that they did not find a statistically significant increase in granzyme B positive cells, correct?

MS. SUTTON: Objection, form.

A. That is correct. I don't think in all cases you can equate statistical significance with clinical or pathophysiologic importance.

Q. Objection, non-responsive.

You did not report the finding of

the granzyme B plus cells in your report, correct?

MS. SUTTON: Objection, asked and answered.

A. That is correct.

Q. And then when it got to FoxP3 positive cells, those are also a marker of regulatory T cells?

A. That is correct.

Q. They help reduce inflammation?

A. That is their role, to try to balance out inflammatory conditions, inflammatory areas.

Q. And if those cells are decreased, that can result in more inflammation and thus more enteropathy?

MS. SUTTON: Objection to form.

A. So there are multiple pathways for unchecked inflammation. One of those is through decreases in regulatory T cells which would lead to unchecked inflammation.

The other way is that you have some much proinflammatory medias that it overwhelms the ability of the T regulatory cells to balance that out. And that's actually what you see in

celiac disease. It's what you see often in inflammatory bowel diseases.

Paradoxically, there's an increase in the anti-inflammatory-type regulatory suppressor T cells despite overall having marked inflammation. This just is a suggestion of the body's inability to respond and adapt with whatever is triggering the inflammation.

Q. And the experiment that's identified here in Exhibit 17 showed that olmesartan resulted in a decrease of the FoxP3 cells, correct?

MS. SUTTON: Objection, form.

Q. Oh, sorry. Wrong. They found an increase in FoxP3 cells.

A. That is correct.

Q. And you do not discuss that in Exhibit 1 either, correct?

MS. SUTTON: Objection, form, misstates --

A. No, I did not. That is not part of my report.

Q. Then we get to their analysis of what's called TGF beta. You agree that the immune regulation in the intestine is crucially

dependent on TGF beta?

A. TGF beta is an important cytokine.

MS. SUTTON: I'm sorry. Object to form on that question. Go ahead.

A. TGF beta is an important cytokine.

Q. And you recall back in 2012 when the Mayo Clinic first published their study that they speculated that a plausible mechanism of action would be inhibition of the TGF-beta signaling?

MS. SUTTON: Objection, form, foundation.

A. Yes, as an important regulator of inflammation, it was a logical supposition at the time when there was no data, pathophysiologic data, to support or refute it.

Q. And Exhibit 17 actually refutes that speculation?

MS. SUTTON: Objection, form.

A. It is. It was why that specific cytokine was looked at in the study and was found not to play a role.

Q. So you agree that TGF beta does not play a role in the mechanism of action for olmesartan enteropathy?

A. Yes, the inflammation seems to occur in a TGF-beta independent fashion.

Q. So having looked at several of these items that were studied in Exhibit 17, tell us what is your proposed theory of a biological mechanism of action?

A. So based predominantly on the Marietta paper and what we know about celiac disease, which is, again, probably the closest analogous condition, what likely happens is that olmesartan, either acting alone or in conjunction with another protein, be itself or foreign, is able to activate IL-15 as part of the innate immune system. IL-15 serves as a keystone between the innate immune system, which is sort of the primitive immune system that allows us to react quickly to viruses and other pathogens, and the adaptive immune system that is responsible for antibody formation and develop very specific cellular responses.

By increasing IL-15, you produce an enteropathy. Likely secondary to that you have a breakdown in the tight junctions that link the cells of the epithelium which allows then an influx of other foreign antigens, as well as

tissue mediators, out into the lumen of the intestine exacerbating damage and together creating all the symptoms.

So almost any time you see too much IL-15 you'll see inflammation.

Q. Okay. And what this study found was increase of IL-15 in olmesartan patients in the epithelium, correct?

A. That is correct.

Q. They did not find an increase of IL-15 in olmesartan patients in the lamina propria, correct?

A. Yes, they didn't find a significant increase. It's interesting that you do see a number of the olmesartan cases where -- which have IL-15 levels in the lamina propria which is significantly beyond anything you see in the off olmesartan group, and so this suggests this might just be a sample size issue. But either way, even in celiac disease you see cases where IL-15 levels are increased only in the epithelium. So it's not -- I don't see this as in any way sort of refuting the importance of IL-15 in this model.

Q. In the celiac disease patients

that in a very large sample even a small statistical difference could be meaningful.

So I think there is a -- there's actually a lot. If you look into the medical literature, there's a lot of controversy about how and when statistical tests are used.

In this case, looking at the graph of IL-15 and the lamina propria, you see three cases that are clearly above anything. You know, if you look at just those cases that are clearly above everything. Yes, there are cases without increased IL-15 in the lamina propria, but that doesn't suggest that there are no cases with increased IL-15 in the lamina propria.

Q. Objection, non-responsive.

MS. SUTTON: Opposed.

Q. Look at Exhibit 17, page 5, top right-hand side. They're talking about Figure 5c. They say "shows that IL15R is not significantly increased by lamina propria cells, but is significantly increased by epithelial cells while on olmesartan."

Do you agree with that finding?

MS. SUTTON: Objection to form, asked and answered.

A. Yes, the statistical test they did was appropriate. However, you clearly see by looking at the graph that there are individuals with increase.

So looking at it as a group, there is no significant difference. Looking at individuals, there are individuals with increased IL-15 levels both in the lamina propria and in the epithelium.

(Whereupon, Deposition Exhibit 21, "IL-15: a central regulator of celiac disease immunopathology," Abadie, et al, was marked for identification.)

BY MR. CHRISTIAN

Q. One of the articles that you include on your reference list I've marked as Exhibit No. 21, which is an article by Abadie and Jabri from 2014 entitled "IL-15: a central regulator of celiac disease immunopathology," correct?

A. That is correct.

Q. And if you turn to page 6, the top of page 6 of Exhibit 21, there's a discussion of IL-15 expression in celiac disease, correct?

A. That is correct.

Q. It says, "The chronic upregulation of IL-15 in the epithelium and in the intestinal lamina propria is a hallmark of the disease and correlates with the degree of mucosal damage."

Do you agree with that statement?

A. I do.

Q. And then down below it says, "Conversely, a high number of celiac disease patients on a gluten-free diet maintain high levels of IL-15 expression in the epithelium, suggesting that dysregulated expression of IL-15 in the epithelium is insufficient to induce villous atrophy."

Do you agree with that?

A. So, yes, I think in celiac disease -- well, you know, that's an interesting statement that whether or not -- I mean, it -- so it's clearly true, and Dr. Jabri has done most of this work, that in people with treated celiac disease still see increased levels of IL-15 in the epithelium but not in the lamina propria.

Again, whether that -- that is not necessarily -- I think they -- to be honest, I think they overstate that a little bit, in that you need -- you know, that gluten is what you

need to induce -- you still have EL-15, but it's the gluten plus the EL-15 that triggers the epithelium damage. It's not saying that the EL-15 in the lamina propria is actually what causes -- induces the villous atrophy. So I think they actually don't discuss the gluten -- they don't make it as clear the gluten component of this as you might expect.

Q. So the EL-15 expression in celiac disease, you disagree with the authors of Exhibit 21 that only having expression of IL-15 in epithelium is insufficient to induce villous atrophy?

MS. SUTTON: Objection to form, misstates testimony, asked and answered.

A. Clearly on a gluten free diet you still have persistent -- typically a patient on gluten free diet will have -- will heal over time, their intestine, and resolve their villous atrophy, and even in those cases, you still have IL-15 in the epithelium. So IL-15 alone in the epithelium in celiac disease in the absence of gluten is not enough to cause villous atrophy.

Q. And that same expression is exactly what they found in the Marietta paper where they

Do you agree that's what they wrote?

A. So in this article, they show that olmesartan, unique among the ARBs tested, has this association, and they show some of the ways that olmesartan can cause some of the pathology -- that could cause this pathology.

So they do write that more -- that only olmesartan is causing all the pathologies, but they do show that olmesartan is causing pathology.

Q. And you agree that many more experiments need to be done?

A. I think we would learn more about the way that olmesartan causes enteropathy by doing more experiments. I don't think more experiments need to be done to show that olmesartan causes enteropathy.

Q. Dr. Leffler, did you in your review of the scientific literature involving olmesartan research or review any articles involving anti-inflammatory effects of olmesartan?

MS. SUTTON: Objection, form.

A. I have looked -- I have read and reviewed articles relating to the systemic and anti-inflammatory effects of olmesartan.

Q. Anti-inflammatory effects of olmesartan?

A. Correct.

Q. And so you recognize that there have been studies that have been done and published that do show anti-inflammatory characteristics of olmesartan?

MS. SUTTON: Objection, form, asked and answered.

A. Yes, systemic anti-inflammatory effects have been found, although they don't appear to be clinical significant, but they -- again, systemically. These are not in the intestine.

Q. Do you know how many -- in how many different organs olmesartan has been shown to have anti-inflammatory effects?

MS. SUTTON: Objection form, no foundation.

A. I do not have a number of organs.

Q. And do you have any biologically plausible explanation of how olmesartan can cause an inflammatory response in some people and an anti-inflammatory response in others?

MS. SUTTON: Objection, form, no

your report, correct?

MS. SUTTON: Objection, form.

A. We have done some experiments with IL-15 in my own laboratory and in my own research as well.

Q. But you've done no research in your laboratory regarding IL-15 and the effect of olmesartan on IL-15, correct?

A. That is correct.

Q. I'm about to start another section. It's up to you as to what you want to do.

MS. SUTTON: You know, it's 12:27. We've been going an hour and fifteen. It's time.

(A lunch break was taken.)

BY MR. CHRISTIAN

Q. Dr. Leffler, we're back from a lunch break. Are you ready to proceed?

A. I am.

Q. You reviewed in this case a series of MedWatch forms from the Daiichi-Sankyo safety database, correct?

A. Correct.

(Whereupon, Deposition Exhibit 23, 11/1/16 to Dr. Leffler from Dr. Kessler, was marked for identification.)

BY MR. CHRISTIAN

Q. I've marked as Exhibit 23 a letter dated November 1st, 2016, from Dr. David Kessler to you. And you received this letter sometime after November 1st?

A. Yes.

Q. Were you expecting this letter from Dr. Kessler? Did you know it was coming?

A. Yes, I was planning on reviewing MedWatch forms.

Q. And you were planning on reviewing MedWatch forms 'cause you had been asked to do that by plaintiffs counsel?

A. I had been asked to do that as part of David -- to confirm that the MedWatch forms pulled by Dr. Kessler were accurate and represented cases of olmesartan enteropathy.

Q. So had you already spoken with Dr. Kessler before you received Exhibit 23?

A. No, I had not.

Q. But you were expecting it because of conversations with plaintiffs counsel?

MS. SUTTON: That's yes or no.

A. Yes.

Q. So you received this letter, and it

says, "Enclosed are 62 FDA MedWatch reports." So was there physical copies of the 62 reports attached to this letter?

A. Yes, there were.

Q. And you see in Exhibit 23 that those 62 come from a total of approximately 9,540 MedWatch reports concerning olmesartan, correct?

A. Correct.

Q. And then Dr. Kessler in Exhibit 23 describes the selection criteria for the 62 MedWatch reports, correct?

A. Correct.

Q. And because you had not had any conversation with Dr. Kessler prior to receiving this letter, you did not have any input on this selection criteria, correct?

MS. SUTTON: Objection form, foundation.

A. Correct.

Q. And were you asked by Dr. Kessler to confirm the selection criteria he used to narrow the MedWatches down to 62?

MS. SUTTON: Objection, form.

A. Yeah, I -- I know that -- so my recollection was that Dr. Kessler suggested these

terms, and I believe -- and -- yeah. Actually, I don't -- I don't recall to be honest.

Q. Do you know where Dr. Kessler came up with the selection criteria?

A. My understanding is he came up with these selection criteria from his review of the literature.

Q. Okay. And do you know the actual process as to how Dr. Kessler searched the 9,540 MedWatch reports?

A. I'm not familiar with the logistics of MedWatch searches.

Q. And you did not confirm this -- strike that.

You didn't go back yourself on to a database and run this search criteria to come up with the same 62, correct?

A. No, I did not.

Q. Okay. And you were asked by him to provide your clinical opinion on whether the presentation of symptoms in each of these patients after taking olmesartan is consistent with the clinical syndrome of olmesartan-associated enteropathy?

A. That is correct.

Q. And is that different than actually looking at the MedWatch and diagnosing a patient with sprue-like enteropathy?

A. So in diagnosing a patient --

MS. SUTTON: Objection, form. Sorry.

A. So making a diagnosis with the patient implies you're working with the patient at the time to determine the cause, that's something you do in clinical practice.

When I looked over these forms, I confirmed that they were consistent and cases of olmesartan-induced enteropathy.

Q. So in looking at the MedWatch forms, you did make a diagnosis of sprue-like enteropathy?

A. Yes. When looking at all these cases, I considered the different causes of enteropathy, made a differential, ruled out other plausible alternatives, and determined they were indeed caused by olmesartan enteropathy.

Q. Did you review any MedWatches other than these 62?

A. These were the only MedWatch forms that I reviewed.

(Whereupon, Deposition Exhibit 24, Dr. Leffler's handwritten notes, was marked for identification.)

BY MR. CHRISTIAN

Q. And Exhibit 24, are these your handwritten notes that you took while you were analyzing the 62 FDA MedWatch forms?

A. That is correct.

Q. Okay. Did you take any other notes besides what's indicated on Exhibit 24?

A. No, these are all of them.

Q. Okay. And when you had your phone conversation with Dr. Kessler on November 22nd, did you discuss your analysis of the MedWatch forms with him?

A. We did.

Q. Did Dr. Kessler indicate any disagreement with your analysis?

A. No, he did not.

Q. Did you talk with any other expert for the plaintiffs regarding your MedWatch analysis?

A. No, I did not.

Q. You are using your analysis of these 62 MedWatch forms to support, verify your

overall general causation opinion in this case?

MS. SUTTON: Objection, form.

A. Yes, these cases -- my review of these cases was fully consistent with my clinical experience and reading of the medical literature.

Q. And while you were going through these 62 MedWatch reports, there were several things that you knew in your head at that time.

Number one, you knew that Dr. Kessler -- you knew he was an expert retained by the plaintiffs in the Benicar litigation, correct?

A. Correct.

Q. You knew that he had done a search of MedWatch forms and sent you 62 of them, correct?

A. Correct.

Q. You knew about the Mayo 2012 article discussing sprue-like enteropathy associated with olmesartan, correct?

A. Correct.

Q. And you knew that there were thousands more MedWatch reports that you did not review, correct?

A. Correct.

Q. That corresponds with number 25 on your Exhibit 24?

A. Okay.

Q. Is that right?

A. That looks correct, yes. It looks correct.

Q. And here the preferred terms were -- celiac disease was the first one, correct?

A. Let's see. Correct.

Q. And you understand that Exhibit 26 was a report by a consumer, correct?

A. Let's see.

Q. If you look on the --

A. It says a spontaneous report by a consumer.

Q. Okay.

A. Yeah, agreed.

Q. And as a physician, would you agree that typically you would get a higher level of information from a report from a physician versus a consumer?

MS. SUTTON: Objection, foundation, form.

A. You know, I think, unfortunately,

you know, especially with things that physicians are compelled to do like this, I think you can get sometimes excellent data from patients, and you can get limited data from physicians who are busy doing other things, and sometimes the opposite. So I think there's overlap.

Q. So in this case, where you indicate that it's a positive rechallenge, the patient indicated that after they began taking Benicar the experience of feeling like a sick puppy. Do you see that?

A. I do.

Q. Described as low blood pressure, feeling exhausted and breaking out in a sweat. Those are not characteristic examples of sprue-like enteropathy, are they, Dr. Leffler?

MS. SUTTON: Objection, form.

A. Well, low BP is one of the first signs you get when you are -- when you decrease intravascular volume. So you have fluid leaking out of your blood vessels into your intestines, so. You know, syncope is commonly -- so passing out due to low blood pressure is commonly seen with inflammatory GI disorders. So the low blood pressure is. The feeling exhausted is fatigue.

Again, fatigue is a very common symptom that you see across many of these reports, and often does -- you see that in celiac disease as well. It often comes on even before the -- before frank diarrhea.

Q. So, Dr. Leffler, it's your testimony that people taking a anti-hypertensive medication that if they have low blood pressure that's a characteristic of sprue-like enteropathy?

A. By itself you couldn't say anything about the low blood pressure, but again, in that situation where a patient has clear symptoms of olmesartan enteropathy with dehydration and diarrhea and renal function that resolved when they were -- with dechallenge, when the olmesartan was taken away, and then had recurrent symptoms again even at low doses, and especially with a second challenge had dry heaves, vomiting as well -- dry heaves would be vomiting without actually throwing anything up -- would be fully consistent with rechallenge.

Q. Well, you see the consumer down at the bottom reports that the celiac disease has not resolved. So that would not be a true

rechallenge, would it, Doctor?

A. So, unfortunately, and you see this across many cases, that celiac disease is a lifelong disorder. So patients who are -- and, again, I've seen this in cases myself, that people continue with the idea that they have celiac disease and continue on a gluten-free diet thinking that they need it, even though it was never really the case in the first place. So the patient would be totally right, and I'm sure his physician told him that, is that you have celiac disease, and now you will have it for the rest of your life, and unless told otherwise that you actually don't have celiac disease, you wouldn't expect a patient to understand that that was actually a misdiagnosis. It's not that it was resolved. It was just never really the case in the first place.

Q. Doctor, you didn't talk to the patient that reported the symptoms in Exhibit 26, did you?

A. I did not.

Q. Okay. And is it your testimony that companies should look behind a report that someone's continuing to have celiac disease and

disregard that report that they're still having symptoms?

MS. SUTTON: Objection, form.

A. So I don't see where it says that he's having symptoms. It just says that he has celiac disease. That is not the same thing. He had symptoms when he was on the olmesartan, and he didn't have symptoms when he was off the olmesartan. He had symptoms when he started the olmesartan again twice. At this point all it says is that he carries with him a diagnosis of celiac disease, which may or may not be accurate, but there's actually no information about whether or not he has ongoing symptoms.

Q. And do you see where the company asks for additional medical history but the patient refused permission for the company to contact the healthcare provider?

A. I do see where it says that.

Q. Is that -- do you place this at a lower level of evidence based upon the fact that we were unable to contact the healthcare provider to get additional information?

MS. SUTTON: Objection, form.

A. So it is always helpful to have

more information, but I think this report is perfectly consistent with olmesartan enteropathy even with the information provided.

(Whereupon, Deposition Exhibit 27, MedWatch Report No. DSU-2009-001282 (OLM-DSI-0004762639-R - 640-R), was marked for identification.)

BY MR. CHRISTIAN

Q. And I'm handing you Exhibit No. 27 to your deposition, another MedWatch form from the group of 62, manufacturer report No. DSU-2009-1282.

Do you see that this was a report also by a consumer?

A. I do.

Q. And that the event is celiac disease?

A. That is what is reported there.

Q. And here on the MedWatch form, Exhibit 27, under Box 5 and 8, there is no check box for event abated or event reappeared; is that correct?

A. That is correct, nothing is checked.

Q. But you have changed that in your

analysis to say that Exhibit 27 does indicate positive dechallenge and rechallenge.

A. I do. If you read the description, the patient was taking olmesartan and experienced vomiting and diarrhea. The patient states that she experiences an episode every time she takes Benicar. So the only way to have an episode every time you take Benicar is if you don't have an episode in between when you're not taking Benicar, otherwise you just have episodes.

Q. Well, you don't know what other medications this patient was taking, do you?

A. I only know what information is provided in this report.

Q. And there's nothing under other relevant medications, right?

MS. SUTTON: Objection, form, asked and answered.

A. But, again, there is -- but there's stated evidence that she had vomiting, diarrhea then gets this episode, vomiting and diarrhea, every time she takes Benicar. So, again, the dechallenge and rechallenge is very clear from this report even without that.

Q. You don't know how or whether this

person is being exposed to gluten, do you?

MS. SUTTON: Objection, form.

A. So we don't know whether she truly has celiac disease, and we don't know if she has celiac disease whether she's being exposed to gluten. However, the chances that she only gets exposed to gluten or she gets exposed to gluten every time she gets exposed to Benicar and that happened to be happening at the exact same time would stretch plausibility.

Q. Exhibit 27 is lacking a lot of information; isn't that right?

A. There are other reports with more information than this one, I agree.

Q. We don't know in Exhibit 27 what the dose, the date of therapy or the indication, correct?

MS. SUTTON: Objection, form.

A. Agree, but there's no evidence that there is a dose response that's discernible in clinical practice or that there's a difference with indication. And as long as you've been on it for, as I said, more than one month, so a long enough time within the realm of the cases we see with, in some cases that are documented

olmesartan enteropathy. It wouldn't change my impression to know whether it had been one month or six months or five years on olmesartan.

Q. And you would not base an opinion that the patient reporting these symptoms in Exhibit 27 has sprue-like enteropathy based solely on Exhibit 27, would you?

MS. SUTTON: Objection, form.

A. Can you restate the question?

Q. Yeah. If all you had ever looked at was this, Exhibit 27, you would not be able to say to a reasonable degree of medical certainty that this patient has sprue-like enteropathy?

MS. SUTTON: Objection, form.

Q. Only using this form and not the other information that you reviewed.

A. There really is no plausible alternative for somebody who gets diarrhea and vomiting episodes every time they take olmesartan other than olmesartan enteropathy.

Q. So this patient in Exhibit 27 that was diagnosed with celiac disease, based upon the information on this two-page form, you'd be comfortable giving her a diagnosis of sprue-like enteropathy?

MS. SUTTON: Objection, form.

A. Yes. If I was to see this patient in my clinic or in, to be honest, in my personal life, I would highly recommend she revisit the diagnosis of celiac disease to see whether that's real because the information provided is much more consistent with olmesartan enteropathy.

Q. And that's what I was asking you. Instead of diagnosing her with sprue-like enteropathy, you would get her to go and try to verify the celiac disease diagnosis, correct?

MS. SUTTON: Objection, form, misstates testimony.

A. No, she has olmesartan enteropathy based on her symptomatic response. Whether or not she could potentially in those rare cases also have celiac disease would, you know, be reasonable to re-evaluate. But in most cases, if they have a response and they're feeling fine off of olmesartan, and they only get sick when they're on olmesartan, and most people with celiac disease get exposed to gluten accidentally every now and again, and if the only episode she's getting when she's getting sick are clearly the days when she's tried to take olmesartan

again, there would be no reason to suspect celiac disease.

Q. For these individual case reports, we never know what you might call a counterfactual scenario, in that we don't know what would happen if these exact same patients were not taking olmesartan, do we?

MS. SUTTON: Objection, form.

A. Right, we have no idea what would -- if they never took olmesartan, then we wouldn't know anything about the patients really to make any logical supposition.

Q. And you wouldn't diagnose a patient with sprue-like enteropathy without seeing what medications that they're taking, would you?

MS. SUTTON: Objection, form, foundation.

A. Again, if the only thing that is changing and the only thing that we have evidence is changing is the taking of Benicar, the not taking of Benicar, and the symptoms are tracked to that exposure, then it really wouldn't -- if they're on NSAIDs, chronically, or even intermittently, if the exposure of the olmesartan is linked to the symptoms, then it really becomes

irrelevant what else, what other medications they're on.

Q. So if a patient comes in your office, you don't even ask them what other medications they're on because it's not relevant; is that what you're saying?

MS. SUTTON: Objection form, misstates --

A. No. Part of a good medical history, you would take a full -- you would learn about past medical history, past social, family history, you hear about medications, but to be honest, none of that would change the clinical diagnosis of olmesartan enteropathy.

Q. And the good medical history that you just discussed is not contained in Exhibit 27, is it?

MS. SUTTON: Objection, form.

A. It is not, but in a case with rechallenge, then it becomes secondary to making that initial diag- -- that diagnosis.

Q. If this particular patient was taking NSAIDs for cyclical pain that happened to occur at the same time that she was taking olmesartan, that would be a possible cause of her

symptoms, correct?

MS. SUTTON: Objection, form.

A. So I would first just point out that NSAIDs, while they do cause small intestinal damage, it is distinct in that it usually -- if anything, it causes bleeding or ulcers. Vomiting and diarrhea happen, but they are very uncommon, especially vomiting with NSAIDs. So this would still be much more consistent with olmesartan enteropathy, even if there was another medication that for some reason happened to be taken and taken off around the same time.

We have no evidence of that, and so there's no reason based on what -- the information here to question the diagnosis of olmesartan enteropathy.

Q. And you see that the company requested further medical information but the patient refused permission to contact the health care provider?

MS. SUTTON: Objection to the form.

A. That is written on the report.

Q. And do you know how many MedWatch reports did the patient refuse permission for the company to contact the healthcare provider to get

additional information?

A. I don't have any information about that.

(Whereupon, Deposition Exhibit 28, MedWatch Report No. SU-2005-004027 (OLM-DSI-004773852-R - 853-R), was marked for identification.)

BY MR. CHRISTIAN

Q. I've marked as Exhibit 28 to your deposition another MedWatch form that you reviewed. It's manufacturer report No. SU-2005-04027.

This is a report by a consumer, correct?

A. It says serious report from a consumer.

Q. Okay. And she had been diagnosed with celiac disease, correct?

A. Let's see. Yes, it says she was diagnosed with celiac, that's correct.

Q. And the main symptom that she experienced was dehydration, correct?

A. It says dehydration requiring two separate hospital admissions, hospitalized due to dehydration. So the dehydration was the reason

for the hospitalization, but the symptom was actually -- she reports as barely being able to keep food down and throwing up. So --

Q. And what you just read, the "gone five weeks barely being able to keep food down," part of that five weeks was during the period when she was not on olmesartan, correct?

MS. SUTTON: Objection, form, foundation.

A. I don't know that that's entirely clear from the way it's written.

Q. Okay. Unclear, I'll take that.

On the --

MS. SUTTON: Objection to the colloquy.

Q. A few sentences up from the end it says, "At this time, Benicar remains discontinued." Do you see -- "the dehydration had resolved," right?

A. Correct.

Q. But the reporter did not know the status of her low blood pressure, nausea and vomiting. So all of those things could still have been going on, correct?

MS. SUTTON: Objection, form,

foundation.

A. So this was -- the report must have been not directly from the consumer 'cause she would obviously know whether her, nausea and vomiting, but from the consumer through a healthcare provider or medical representative.

Q. Do you recall the question?

A. So the question was whether they are ongoing. Well, it does say -- it does say they are known, but there's been no further history of dehydration or passing out.

Q. And this patient had a medical history of passing out with penicillin, correct?

A. That is stated, passing out with penicillin. Although -- well. Although dehydra- -- passing out could have been an anaphylactic response to penicillin. It would not be associated with dehydration. So at this time, Benicar remains discontinued and the dehydration has resolved.

Q. But we don't know whether or not the low blood pressure, nausea or vomiting had resolved, do we?

A. Well, the low blood pressure is hard to determine 'cause she was started on other

blood pressure medications. But the dehydration -- the dehydration, which is actually what made this a serious adverse event, with hospitalization has resolved. And as we see with a lot of patients with severe small intestinal injury, they may have some continuing GI symptoms related to post-inflammatory, post-infectious irritable bowel syndrome. It's fairly well-known that people who have highly damaged intestine will have some ongoing symptoms because of the disruption of the enteric nervous system. I got to slow down.

So -- you know, and that's true from what we see, again, not just with olmesartan but across GI diseases, you can continue to have some nausea, some alternating bowel habits even after the malabsorption resolves, even after the intestine is healed, at least the mucosa and the villi have healed, due to this post-inflammatory -- post-inflammatory irritable bowel syndrome, functional bowel disorder.

So what I would think is that even if it said she's still having some nausea, the fact that dehydration leading to hospitalization has resolved is convincing evidence of

dechallenge.

Q. Objection, non-responsive.

MS. SUTTON: Oppose.

Q. Dr. Leffler, it's a pretty simple question, I think. Exhibit 28. What we know from this reporter is that after she stopped taking Benicar is that we don't know whether or not she was still having low blood pressure, nausea or vomiting.

MS. SUTTON: Objection, form, asked and answered.

Q. You don't know that, do you?

A. I do not. The most important symptom that resolved is the dehydration.

Q. I'm not asking about the most important symptom, Doctor. I'm not asking about that. You've talked had dehydration several times now.

The simple question is, you don't know whether nausea and vomiting and low blood pressure had discontinued or not?

MS. SUTTON: Objection, asked and answered.

A. That information is not in the report. It does not change my assessment of the

case.

(Whereupon, Deposition Exhibit 29, MedWatch Report No. DSM-2010-01260 (OLM-DSI-004756139-R - 140-R), was marked for identification.)

BY MR. CHRISTIAN

Q. Exhibit 29 is an additional MedWatch form, manufacturer report DSM-2010-01260.

Do you see in this report that -- first of all, there's just an extremely low amount of information in this report. You'd agree with that?

A. Yes, I do agree there's not -- I do agree.

Q. There's nothing filled out in Box 6 for relevant tests or laboratory data or Box 7 on other relevant history or Box 10 for concomitant medical products and therapy dates, correct?

A. That is correct.

Q. We don't know the olmesartan dose?

A. That is correct.

Q. And we don't even know the start date of olmesartan, correct?

MS. SUTTON: On this form?

MR. CHRISTIAN: On the form.

A. Yeah, under -- let me see. Yes, that information is not listed on this form.

Q. How much time did it take you between November 1st and November 22nd to review these 62 MedWatch forms?

A. I don't recall. It would be a number of hours.

Q. Did you do it at multiple settings?

A. Yes, this was not all in one setting.

(Whereupon, Deposition Exhibit 30, MedWatch Report No. DSM-2010-01269 (OLM-DSI-004756141-R - 142-R), was marked for identification.)

BY MR. CHRISTIAN

Q. I'm marking Exhibit No. 30. It's another MedWatch form, manufacturer number DSM 2010-01269.

This is a report by a consumer, correct?

A. That is correct.

Q. I haven't been noting this previously, but this is one that's a report from outside the United States, correct?

A. It says from Germany.

Q. Yeah. And here the MedWatch form, Exhibit 30, does not have a check off for event abated or event reappeared, correct?

A. It is not checked off in that box, correct.

Q. And all we know is that -- or the last sentence there we know that there's no information regarding the outcome of the events, and that would make sense that there would not be a positive rechallenge if we don't know the outcome of the events, correct?

MS. SUTTON: Objection, form, foundation.

A. So it says very clearly on the front of the page, after re-exposition on three -- it says after re-exposition, but I think we can infer after re-exposure -- on three different days between June 2010 and 11 September 2010, he experienced diarrhea and vomiting in each case. And then after that it goes on to say there's no information regarding the outcome of these events. But he has -- these are three separate events with three separate episodes, again implying resolution between those cases,

otherwise it would say he experienced chronic diarrhea and vomiting between June and September. So these are three distinct events with vomiting. So this is very clear documentation to me of rechallenge effect.

Q. And you're implying resolution of symptoms after the September 11, 2010, date, correct?

A. Well, it specifically says on three different days he experienced diarrhea and vomiting. That doesn't say three months of diarrhea and vomiting on which --

Q. You don't know, Doctor, after September 11, 2010, if there was 30 more days where he decided to take olmesartan and didn't have these symptoms, do you?

A. No, but three separate challenges with symptoms that are highly consistent with olmesartan enteropathy are extremely compelling data, and you would expect that few people would keep doing that over and over again, subjecting themselves to those symptoms indefinitely.

Q. Well, you're implying that they continued to have those symptoms after subsequent re-exposure. That's something we don't know off

Exhibit 30.

MS. SUTTON: Objection, form, misstates testimony.

A. So these forms, obviously, only go up to the time they're reported. We can never know what happens in the future.

However, during the time that's covered in this report form, the three episodes that are reported only happen on the three -- are said to happen on the days he took olmesartan. So for the time period covered in this, he had olmesartan enteropathy. We don't --

Q. And we don't -- there's no information regarding the outcome of the events, correct?

A. There is no information provided after the last -- after the report.

Q. One of the reports you excluded out of the 62 was because the patient had just been on olmesartan for a week; is that correct?

A. Yeah, it was for a short period of time. I don't recall. I think it was one. It sounds about one week.

Q. I think in your report you indicated it was a week.

that doesn't apply to people who have a clinical response to cessation of olmesartan 'cause then you do know what the cause is. But in other cases where they're not on olmesartan and there's villous atrophy, then it is -- then you have to rule out other causes, and you don't always have a definitive diagnosis at the end of that evaluation.

Q. So if someone's on olmesartan, that overrules everything else, and they couldn't possibly have non-celiac enteropathy caused by something else?

A. No.

MS. SUTTON: Objection, form.

A. When patients have a clinical response to olmesartan withdrawal, then there is no reason to do an extensive evaluation for other causes because they've already clinically responded.

Q. And you recall the Aziz paper we talked about earlier where they looked at the 200 patients, looking at the biopsy and the causes of non-celiac enteropathy, and they found in that group a large percentage of patients where we don't know the cause of the non-celiac

BY MR. CHRISTIAN

Q. Exhibit 31 is another one of the MedWatch forms that you reviewed. Manufacturer report number SU 2006-005527.

This is one where the preferred term reported was tropical sprue which is something we talked about earlier is a cause of villous atrophy, correct?

A. That's correct.

Q. And in this patient, on Exhibit 31 the check box for rechallenge was no, correct?

A. Reappeared after reintroduction. In Box 8 you're referring to?

Q. Yes.

A. That's correct.

Q. And that's contrary to your finding, correct?

MS. SUTTON: Objection, form.

A. Let me read over the report.

Q. I mean, this wouldn't be in the 62 if you didn't agree there was a rechallenge, right?

A. Yeah, no, I do. Yes, I agree, there was evidence of rechallenge.

Q. Okay. And you see that the

original information was reported by a consumer who talked about traveling to St. Thomas and the Virgin Islands and then was diagnosed with tropical sprue, and that's something that you could recognize could happen, correct?

A. So tropical -- to develop tropical sprue typically requires living in or spending extended periods in endemic regions. A visit to the Caribbean would be highly unusual to result in tropical sprue.

Q. Now, Doctor, did you -- the company you see followed up with additional information from the treating physician?

A. Mm-hmm. Yes, I see that.

Q. And did you review that section?

A. I did.

Q. Okay. And do you see where the physician says that the patient stopped olmesartan on June 1st, 2006?

MS. SUTTON: I'm sorry.

Q. The second sentence. "He," referring to the treating physician, "reported that the patient stopped the medication" --

A. The medication prior to --

Q. -- "prior to his diagnosis of tropical sprue on June 1st, 2006," correct?

A. That is correct.

Q. Okay. And then the physician goes on to tell them that the events of tropical sprue: weight loss, vomiting and diarrhea all began on June 1st, 2006. That is the date that the olmesartan was stopped, so that cannot be a case of dechallenge, rechallenge or even a case of olmesartan enteropathy, can it?

MS. SUTTON: Objection, form, foundation.

A. So what is not clear after the physician indicates that the event was not related to Benicar HCT, as he says, was whether that was restarted at that time. And above you have -- again, this is very clear, the patient reports took one dose of Benicar, and within two to three hours of taking it, experienced the exact same thing of vomiting and diarrhea. So he has multiple rechallenges, and from the patient's report, he took -- it says -- actually, when you go above, "Patient reports that he took Benicar HCT up until that time," which is -- which is a time requiring hospitalization on three separate

occasions.

So, I mean, the patient should be the source of whether they were taking the medications. And, again, with multiple rechallenges, you know, you would really suspect that either the doctor may have said stop it but he didn't or the patient restarted it. It's not entirely clear. But what is clear from the part above is, on each time he took the Benicar, within two to three hours it's the exact same thing, that recurrent syndrome of vomiting and diarrhea. And as he reports, the patient, the vomiting and diarrhea is a violent reaction to the Benicar.

Q. So in your differential diagnosis of reviewing MedWatch reports, if there's a dispute on the facts between what the consumer reported and the treating physician reported, you're going to go with what the consumer reported?

MS. SUTTON: Objection, form, misstates testimony.

A. It depends what the facts are. If the patient said I was taking a medication, and the physician says I told him to stop the

medication, then oftentimes we know patients don't always hear, don't always act on our advice correctly.

If the physician reported a lab value, of course I would take that with more weight than the patient. But in terms of the patient's symptoms and what they were taking, the person actually taking the medication at the time in their own home knows better than any physician.

Q. Well, let me ask you this, if it's accurate that the treating physician reported that the patient stopped medication on June 1st and also that the events of tropical sprue, weight loss, vomiting and diarrhea, all began on June 1st, 2006, this would not be a case of sprue-like enteropathy, if that is accurate?

MS. SUTTON: Objection to form, no foundation.

A. So, again, the report from the patient is clear. It suggests strongly that he was on Benicar at the time when these hospitalizations arose. Yes, if there was reason to suspect that the patient was wrong about what they were taking and the physician was correct

and he had actually been off olmesartan for a period of weeks or months before the syndrome began for the first time, then that initial episode would be suspect. Again, but it wouldn't -- but even that would not deteriorate the quality of the multiple rechallenges.

Q. Objection, non-responsive.

MS. SUTTON: Opposed.

Q. So if a patient stops taking olmesartan and they get symptoms any time in the future after they take stop taking olmesartan, you're going to testify that that's sprue-like enteropathy, Dr. Leffler?

A. No, that's not what I said.

MS. SUTTON: Objection to form, misstates testimony.

A. If the patient --

MS. SUTTON: Sorry, you have to let me finish.

A. Sorry. That's not what I'm saying. However, if a patient -- many things can happen in the past, but if a patient comes in and says, hey, every time I take olmesartan I get vomiting and diarrhea, that is consistent with olmesartan enteropathy.

Q. The information from the patient does not indicate how long they had been in the Caribbean, does it?

A. It does not. It does not.

Q. So they could have been there a sufficient time period to contract this tropical sprue, Doctor?

A. That is possible. But even in people who live in the Caribbean, tropical sprue is a rare entity. And for somebody who clearly is a citizen of the United States, who was there for some length of time, to come back -- and, again, even if we suppose that, then that has no bearing on the rechallenge effect. It doesn't explain why he keeps getting sick when he gets exposed to olmesartan in the future, and that would obviously not be part of the clinical syndrome of tropical sprue.

MS. SUTTON: Can we go off the record for just a second.

MR. CHRISTIAN: Exhibit 32 and then we'll go off.

(Discussion off the record.)

(Whereupon, Deposition Exhibit 32, MedWatch Report No. SU-2004-002638 and attachments (OLM-DSI-0004773653-R - 654-R), was marked for identification.)

BY MR. CHRISTIAN

Q. Exhibit 32, Dr. Leffler, one of the MedWatches you reviewed, SU-2004-0002638.

This is a case you might recall where they were diagnosed with giardia.

A. Correct.

Q. And that's based on a stool test, correct?

A. That is -- I don't remember how it was diagnosed in this or if that was even reported. Giardia -- there's a couple different ways giardias can be diagnosed in general. One is by a stool test. Another one would be by endoscopy. But oftentimes it is diagnosed based on a clinical suspicion, if there's symptoms that sound like giardia and there was a suspected exposure. You see that sometimes in people who have -- say, report going camping, for instance, and drinking stream water.

So I don't recall, and you can please point me to that, if it does say how she

was diagnosed, 'cause it's not -- but I don't recall seeing that.

Q. On the third page in, where you see some handwritten notes on the MedWatch form.

A. Yeah.

Q. First of all, we know that she stopped Benicar on April 5th, 2004, according to the MedWatch form.

MS. SUTTON: Objection, form.

Q. Going back to the first page, under Therapy Dates over on the right-hand side. There's two entries for Benicar 40 milligrams. The first entry is January 22nd, 2004, to April 5th, 2004, correct?

A. Yes, that's correct.

Q. Okay. So at that point in time, she stopped on April 5th, 2004. The date of her giardia diagnosis was April 16th, 2004, correct?

A. Yes, that says -- where does it say the date?

Q. In the handwritten section. Not that handwritten section. No, sorry.

A. Oh, over here. Date of -- yes. 4/16, correct.

Q. And the Flagyl, which is a

prescription for someone with giardia -- an antibiotic, correct?

A. Correct.

Q. -- was started on April 21st, correct?

A. Correct.

Q. And the hospitalization was from April 26th to April 29th, correct?

A. That is correct.

Q. Okay. So she had stopped taking the medication, was diagnosed with giardia, and then started Flagyl, and then went to the hospital, correct?

MS. SUTTON: Objection, form, foundation.

A. So, yes, looking at this, in early April 2004, she developed rampant diarrhea, so the Benicar was discontinued. The rampant diarrhea lasted two weeks. She was then diagnosed -- as we said, we don't know how -- with giardia and prescribed Flagyl.

Flagyl commonly causes gastrointestinal upset. So on top of the rampant diarrhea and the Flagyl effect, she was hospitalized, and then she recovered, and then

with each -- and then she would take Benicar once in a while and get sick or violently ill with diarrhea.

So to me, the obvious explanation clinically is that she was still recovering from olmesartan enteropathy, which we know can take some time, and then she was put on another medication for a diagnosis of giardia, which may or may not have been true, which is a known cause of nausea and stomach upset and loss of taste, and got that much sicker and required hospitalization because of the combination of the two.

And then with the positive rechallenge after that, she had -- she got -- she continued to get sick every time she took the Benicar.

Q. Well, look at the third page, this is all the handwriting, in Exhibit 32.

A. Okay.

Q. Here the consumer is reporting that the Flagyl made her so sick that she was hospitalized for a few days. So now you're going to disregard what the consumer is reporting as being accurate in this MedWatch report?

MS. SUTTON: Objection, form, foundation, mischaracterizes testimony.

A. No, it's clear that she was having the rampant diarrhea before the Flagyl. She took the Flagyl, and the Flagyl on top of the ongoing diarrhea precipitated her going to the hospital. The rampant diarrhea is clearly lasting weeks, two weeks.

Q. Doctor, the report says after she discontinued on April 5th that the event resolved in two weeks, and two weeks would be before the time that she went into the hospital.

Sorry, going back to the page before again. Sorry, the middle of the page. You see right there in the little description part, "58-year-old female reported that she experienced rampant diarrhea within six months of initiating Benicar. The medication was discontinued and the event resolved in two weeks."

So if the event resolved two weeks after April 5th, that would be the 4th she was hospitalized?

A. Yeah, so the diarrhea was -- the rampant diarrhea appears to have been improving

after cessation of the olmesartan, as you would expect. She was then put on this other known gastric irritating medication. And on top of -- and we would not expect the olmesartan enteropathy to resolve within two weeks. The diarrhea might improve substantially, but the olmesartan enteropathy is not going to resolve.

And on top of that, she got the second medication, which it sounds like she didn't really need since the diarrhea was already resolving after she stopped the olmesartan, and then she was hospitalized. And then every time the she took olmesartan after that, she got this stereotypical illness.

Q. So if you had a patient come in and they were diagnosed with giardia, you would not prescribe Flagyl or another antibiotic if they were taking olmesartan?

MS. SUTTON: Objection, form, foundation.

A. Again, we don't know how she was diagnosed, whether that was a presumptive diagnosis.

Q. I'm not talking about how we know.

MS. SUTTON: Were you done with

your answer? I don't think you were done.

A. We can continue.

Q. The hypothetical if someone comes in your office, they've been diagnosed with giardia, you're telling this Jury and these judges that you would not prescribe an appropriate medication for that condition if they were taking olmesartan?

MS. SUTTON: Objection, form, misstates testimony.

A. Yeah, that is not what I'm saying. If the patient had symptoms that were consistent with giardia and had a diagnostic test that showed giardia, regardless of what other medication they were on, I would treat them. But, again, that does not explain the fact that the rampant diarrhea resolved with stopping olmesartan, not with the addition of the metronidazole. As we just said, the metronidazole or Flagyl was put on after the diarrhea was already beginning to resolve.

So the symptoms that actually got her diagnosed in whatever way for giardia were actually already resolving before, which you would not expect if this was truly giardia. And

then, again, she gets the symptoms every time she gets exposed to olmesartan, which is not consistent with, you know, recurrent giardia.

Q. Another equally plausible explanation is that the patient resolved, as it says, completely within two weeks after stopping olmesartan, got giardia, is prescribed Flagyl, and got sick from the giardia or the Flagyl and that's why they went to the hospital.

MS. SUTTON: Objection, form, no foundation.

A. So that might explain -- so at best that would explain the hospitalization, but it doesn't explain the diarrhea or the rechallenge. So, yes, somebody with olmesartan enteropathy at a different point in their history could get giardia. Somebody with olmesartan enteropathy can at some other point in their medical history contract giardia or a pneumonia or many other things, but again, there's a clear withdrawal effect and rechallenge effect.

MR. CHRISTIAN: I think you better take care of your teenager.

MS. SUTTON: Yeah. It will take one second for the call. Do you want to do a

break now? We've been going for an hour and 15.

MR. CHRISTIAN: Sure.

(A break was taken.)

BY MR. CHRISTIAN

Q. Ready to proceed, Dr. Leffler?

A. I am.

Q. If you reviewed a MedWatch report where a woman was taking olmesartan and began having diarrhea, weight loss and vomiting and then stopped taking olmesartan and it clinically resolved, would that be enough for you to diagnose that person with sprue-like enteropathy?

MS. SUTTON: Objection, form, foundation.

A. So for the MedWatch forms that we reviewed, we focussed on ones with rechallenge 'cause not all MedWatch forms have a lot of data, and then rechallenge provides convincing evidence.

In clinical practice, as we discussed, that would be sufficient. So a MedWatch form it would depend what else was or was not included in that form.

Q. So you still could diagnosis someone like that, with sprue-like enteropathy,

even without rechallenge?

MS. SUTTON: Objection, misstates testimony.

A. That is consistent with current medical practice. If sufficient information was available in a MedWatch form about comorbidities, other medications, other things that we would care about clinically, other changes that might have happened at the same time with that dechallenge or might not have, then, yes, it could be convincing, but you would need to know a lot more information.

Q. And if you had more information, what are some -- what else would you need to know about this woman who's taking olmesartan and had vomiting, nausea and then she stopped taking olmesartan and it clinically resolved? What else would you need to know to make a diagnosis of sprue-like enteropathy?

MS. SUTTON: Objection, form.

A. So other helpful pieces of information, and you wouldn't necessarily need all of these, but other things that would be helpful would be other medications that they were on, were any other medications stopped or added

Q. And you recognize that the ROADMAP study is a double-blind, randomized controlled trial, correct?

A. That is correct.

Q. And in the hierarchy of evidence, a randomized controlled trial is the highest level of evidence, correct?

A. So randomized controlled trials are an excellent study design, but they are only as good looking as looking at -- as they're powered for the outcome you're addressing. So they're excellent at looking at -- if they're designed properly, they're excellent for interpreting the primary outcome of the study.

For secondary outcomes and adverse events, they are often insufficient. And this is why we do things like MedWatch reports, 'cause in even the largest clinical trial, randomized clinical trial, pivotal clinical trial, uncommon and unexpected adverse events are often not seen.

Q. Dr. Leffler, you understand what evidence-based medicine is, don't you?

A. I do.

Q. And you agree that a fundamental principle of evidence-based medicine is the

one way to find at least some possibly non-symptomatic patients that might have sprue-like enteropathy?

A. Yes, all these patients had abdominal pain. They all had a reason, a clinical reason, for the endoscopy, but it is a way that you could find histologic changes.

Q. And the authors of this study concluded that there was no statistically significant difference between olmesartan users with abdominal pain and controls for any single histopathological abnormality, correct?

A. That is what they -- yes, they did conclude that in this group of patients all with abdominal pain.

Q. Okay.

A. However, there are, as I report -- as I put into my report, there are interesting trends towards increased amounts of enteropathy, intestinal changes in the olmesartan users compared to the matched controls, either the matched controls or the patients on other ARBs.

Q. Objection, non-responsive starting with the word "however" to the end.

MS. SUTTON: Opposed.

Q. You were talking about the results in Table 2?

A. Correct.

Q. And the fact that the p-value -- well, you agree that they didn't find a statistically significant difference?

A. I agree.

Q. And the p-value of .34, would that mean that there's a 34 percent probability that the result would be completely attributable to chance?

A. That is -- how do I phrase that. Yeah, that's a -- that's a reasonable interpretation of that p-value.

Q. Do you know whether the analysis -- you're talking about the aggregation of histological features at the very bottom of Table 2? Is that what you were pointing out to me a while ago?

A. That's what I refer to in my report, that 50 percent of patients have one or more features of enteropathy compared to 20 percent of matched controls, but it applies across. When you look at villous atrophy and crypt hyperplasia you also see similar trends.

Q. So for this category there at the bottom that you just reference to about the one or more sprue-like features, do you know whether or not that was a predetermined analysis or whether it was a post hoc analysis?

MS. SUTTON: Objection, form.

A. I don't recall.

MR. CHRISTIAN: That was a pretty good question. What's the basis of that?

MS. SUTTON: Compound.

A. So it says here that it is a post hoc analysis.

Q. So that was not something that they had preplanned to do when they were working on some study, correct?

A. That is correct.

Q. And if you look at the matched controls for the olmesartan group versus the matched controls for other ARBs, you would expect the controls to be substantially similar between the two groups, correct?

MS. SUTTON: Objection, form.

A. You mean the healthy controls and the other ARB controls? The matched controls and the other ARB users?

Q. For both groups you would expect those to be similar? If you're trying to find a difference between olmesartan and other ARBs, you would want them to have similar controls between each comparison, right?

A. You would want them -- yeah, you would want -- I mean, if you expect that the other ARBs do not have a response, you would expect that the results in that group would be similar to the matched controls not on ARBs, if that is what your question was.

Q. So if we used the matched controls from the other ARB analysis and switched it to the matched controls from the olmesartan analysis, you'd actually have more people in the control group with one or more sprue-like features than you did in olmesartan users, correct?

MS. SUTTON: Objection, form, foundation.

A. But those are not matched to the olmesartan users, so we don't know what they're not matched on. They could be older. They could be on other medications. You can only match to the group they're matched to. You can't cross

match and expect them to be the same.

Q. But you wouldn't expect the matched controls for the olmesartan to be different than the matched controls for the other ARBs, would you?

A. If there are -- I don't know. Let's see if they report any of that.

So the other ARBs are more likely to be female. Are more likely to be male. Sorry. 45 percent versus 30 percent. So there are significant differences between the other ARBs, just in the simple demographics they put here on Table 1, compared to the olmesartan.

So I think it's hard to compare. That's why they have two separate matched controls. It would have been much easier for them to have one group of matched controls, obviously. It's less work.

Q. Right.

A. But since the olmesartan and non-ARBs looked slightly different, that would not have been appropriate.

Q. And if they would have used just one set of matched controls, then it would have been the matched controls in this study for the

other ARB analysis. Those controls would have had more sprue-like features than the olmesartan users, correct?

MS. SUTTON: Objection, form, foundation.

A. But they're not matched to that population.

Q. I understand that. My question is, if they would have used those matched controls -- well, let me strike it. Rephrase.

The matched controls for the ARB analysis group, on the very bottom group, those are people that are not taking olmesartan, correct?

A. That is correct.

Q. And they're not taking another ARB, correct?

A. That is correct.

Q. And 60 percent of them were positive for one or more sprue-like features on histology, correct?

A. That is correct.

Q. And that is more than the 50 percent with one or more sprue-like features in the olmesartan users, correct?

A. That is correct, except for that -- but it is not a matched population, so you would not make that comparison scientifically.

(Whereupon, Deposition Exhibit 39, "Comparative Effectiveness of Olmesartan and Other Angiotensin Receptor Blockers in Diabetes Mellitus," Padwal, et al, was marked for identification.)

BY MR. CHRISTIAN

Q. Marked as Exhibit No. 39 to your deposition is a study by a Raj Padwal.

A. Mm-hmm.

Q. This study, I did not see you cite this in your report or include it in any of your materials that you reviewed or relied upon.

Have you seen Exhibit 39 before?

MS. SUTTON: Objection, form.

A. Yes, I have reviewed this.

Q. Okay. And is there a reason why you did not include that either in your report or in the materials that you reviewed and relied upon for your opinions in this case?

MS. SUTTON: Objection, form.

A. Yes, the -- I mean, the combination of using non-specific terms for the GI outcomes

foundation.

A. Correct. There is a trend in the adjusted analysis, but it does not reach statistical significance over the study with the relatively short duration of exposure.

Q. So their overall conclusion does not support your opinion of general causation, does it, Dr. Leffler?

MS. SUTTON: Objection, form.

A. So this report, similar to the ROADMAP, does not give -- does not refute the Basson study in any way suggesting that there is an association.

Q. But it also does not support your opinion on general causation?

MS. SUTTON: Objection, form, foundation.

A. While there's no statistically significant, I actually find it meaningful that there's a trend both for GI disease related hospitalization and non-infective enteritis and colitis related admissions in the adjusted analysis, even though this is in a study without a significant enough duration of exposure to really begin seeing the majority, what we believe

to be the majority of olmesartan enteropathy severe outcome cases.

Q. In these large population-based studies, it's important that the reporters of the data report it with respect to whether or not the outcome is statistically significant, correct?

MS. SUTTON: Objection, form and foundation.

A. It is.

Q. And you claim that you were aware of Exhibit 39 prior to writing your report in this case, correct?

A. That is correct.

Q. And now you're saying it's meaningful to your opinion?

A. So what I -- so, as I said, I think it is -- it doesn't change the opinions as I wrote in my draft. It doesn't -- it is -- there is some suggestive things, but they do not reach statistical significance. The fact that they do not reach statistical significance does not make me believe that they do not really exist.

Q. So we have gone through from what I could tell from your reliance materials all the studies that have a control group to them, which

Exhibit C

GE Port J Gastroenterol. 2016;23(2):61–65

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EDITORIAL

Sprue-Like Enteropathy Associated With Olmesartan: A New Kid on the Enteropathy Block

Enteropatia Tipo *Sprue* Induzida Por Olmesartan: Uma Nova Entidade no Campo Das Enteropatias

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Sprue-like enteropathy associated with olmesartan, first identified by our group in 2012,[1] is characterized by chronic diarrhea (often severe) and weight loss that is unresponsive to a gluten-free diet. Laboratory work-up commonly reveals non-specific anemia, hypoalbuminemia, electrolyte imbalance, and vitamin deficiencies, consistent with a severe malabsorption process. Histopathological findings include a combination of duodenal villous atrophy, increased intraepithelial lymphocytes, and a thickened subepithelial collagen layer (collagenous sprue). Histologic changes can be limited to the small bowel, or may include the entire gastrointestinal tract, with findings such as lymphocytic/collagenous gastritis and colitis. Individuals with sprue-like enteropathy associated with olmesartan have negative celiac serology. The majority may have either HLA-DQ2 or DQ8 haplotypes (61–81%).[1] Diagnosis of olmesartan associated enteropathy should therefore be considered in cases of villous atrophy with negative celiac serology (so-called seronegative villous atrophy). Confirmation of diagnosis requires clinical resolution of symptoms after olmesartan withdrawal. Mucosal recovery is also expected within 3–6 months of olmesartan withdrawal and a follow-up duodenal biopsy is reasonable.

Severe sprue-like enteropathy associated with olmesartan appears to be rare although a spectrum of disease severity may be possible.[2] The annual incidence rate of enteropathy in a French population-based study among patients treated with olmesartan for at least 6 months was calculated at 1.3 cases per 1000 individuals per year (95% confidence interval (CI) of 0.5–2.6).[3] This rate is not significantly different from the rate of 0.63 cases of incident celiac disease per 1000 reported by the Mini-Sentinel (95% CI: .38–.99) ($p = 0.16$).[4] The Mini-Sentinel reported that rates of incident celiac disease were of similar magnitude for all angiotensin receptor blockers with, for instance, a rate of 0.43 cases per 1000 (95% CI: 0.33–0.55) for losartan. Mini-Sentinel data therefore suggest that enteropathy may be a class-related drug effect. Such a hypothesis is supported by sporadic case-reports of enteropathy possibly associated with irbesartan,[5] losartan,[6] and valsartan.[7] However, a nation-wide case-control Swedish study failed to show any association between the use of either angiotensin converting enzyme blockers or non-olmesartan angiotensin receptor blockers and subsequent villous atrophy.[8] Thus, there is clear predominance of published data relating olmesartan to enteropathy (Table 1).

Sprue-like enteropathy associated with olmesartan should be ruled out early in the investigation of patients with seronegative villous atrophy. Indeed, a case-series on 72 patients with seronegative villous atrophy found the most frequent etiologies to be seronegative CD (28%), medication-related (26%), unclassified sprue (14%), autoimmune enteropathy (4%), and giardia (4%).[13] Of the

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http://dx.doi.org/10.1016/j.jpge.2016.02.005

Table 1 Case-reports and case-series of sprue-like enteropathy associated with olmesartan published after the Mayo Clinic 2012 original case-series.

Reference number	Author	Country	Date of Publication	Number of cases	Comments
9	Talbot	USA	2012	1	Follow up histology: no
10	Dreifuss et al.	USA	2013	1	Follow up histology: no
11	Nielsen et al.	USA	2013	1	Follow up histology: yes Time after cessation: 3 months Resolution of histologic changes: yes
12	Stanich et al.	USA	2013	1	Follow up histology: no
13	DeGaetani et al.	USA	2013	16	Follow up histology: 2/16 Time after cessation: 12 months Resolution of histologic changes: yes (2/2)
14	Abdelghany et al.	USA	2014	1	Follow up histology: no
15	Tran et al.	USA	2014	1	Follow up histology: no
16	Théophile et al.	France	2014	5	Follow up histology: yes (2/5), no (3/5) Time after cessation: 2 months (2/2) Resolution of histologic changes: yes (1/2), partial (1/2; IELs still present but VA resolved)
17	Gaur et al.	USA	2014	1	Follow up histology: no
18	Fiorucci et al.	Italy	2014	1	Follow up histology: no
19	Khan et al.	USA	2014	1	Follow up histology: no
20	Hartranft et al.	USA	2014	1	Follow up histology: no
21	Ianiro et al.	Italy	2014	3	Follow up histology: 3/3 Time after cessation: 3 months (2/3), not reported (1/3) Resolution of histologic changes: yes 2/3, partial (1/3)
22	Gallivan et al.	Australia	2014	1	Follow up histology: yes Time after cessation: 4 months Resolution of histologic changes: yes
5	Marthey et al.	France	2014	36	Follow up histology: 15/36 Time after cessation: 9 months Resolution of histologic changes: yes (15/15)
23	Scialom et al.	France	2015	7	Follow up histology: 5/7 Time after cessation: 2-7 months Resolution of histologic changes: yes (4/5); one had biopsy while on anti-TNF-αantibodies and olmesartan discontinued with resolution of histologic changes (1/5)
24	Kulai et al.	Canada	2015	1	Follow up histology: yes Time after cessation: 14 weeks Resolution of histologic changes: yes
25	Muñoz- Muñoz et al.	Spain	2015	1	Follow up histology: no
26	Marco-Marqués et al.	Spain	2015	11	Follow up histology: no
27	Heerasing et al.	Australia	2015	1	Follow up histology: yes Time after cessation: 4 months Resolution of histologic changes: yes
28	Fabian et al.	Austria	2015	1	Follow up histology: yes Time after cessation: 2 months Resolution of histologic changes: yes
29	Fukushima et al.	Japan	2016	1	Follow up histology: yes Time after cessation: 11 months Resolution of histologic changes: yes
30	Imperatore et al.	Italy	2016	1	Follow up histology: yes Time after cessation: 8 months Resolution of histologic changes: yes
31	Schiepatti et al.	Italy	2016	2	Follow up histology: Yes (2/2) Time after cessation: 2 months (2/2) Resolution of histologic changes: yes (2/2)
3	Esteve et al.	Spain	2016	20	Follow up histology: yes (19/20) Time after cessation: 3–12 months Resolution of histologic changes: yes (18/19), no (1/19)

medication-related seronegative villous atrophy, roughly 84% were attributed to olmesartan.[13] Early identification of individuals with sprue-like enteropathy associated with olmesartan is clinically relevant as symptoms can be severe and/or life-threatening with expected clinical response within days of olmesartan withdrawal.[1]

In this issue of *GE Portuguese Journal of Gastroenterology*, case reports by da Silva et al.[32], Carneiro et al.[33] and Eusébio et al.[34], highlight the importance of considering sprue-like enteropathy associated with olmesartan when approaching a patient with seronegative villous atrophy and provide further information to aid in diagnosis of this emergent disease.

In their case-report, da Silva et al. outline a practical algorithm to approach diagnosis of seronegative villous atrophy that does not respond to a gluten free diet.[32] The first proposed step following testing for celiac serology is a review of the patient's medication list. In the four cases reported in this issue, symptoms resolved within 48 h to one week of discontinuation of olmesartan.[32–34] Trialing a patient off of a medication early on in the evaluation of seronegative villous atrophy could therefore provide both a rapid

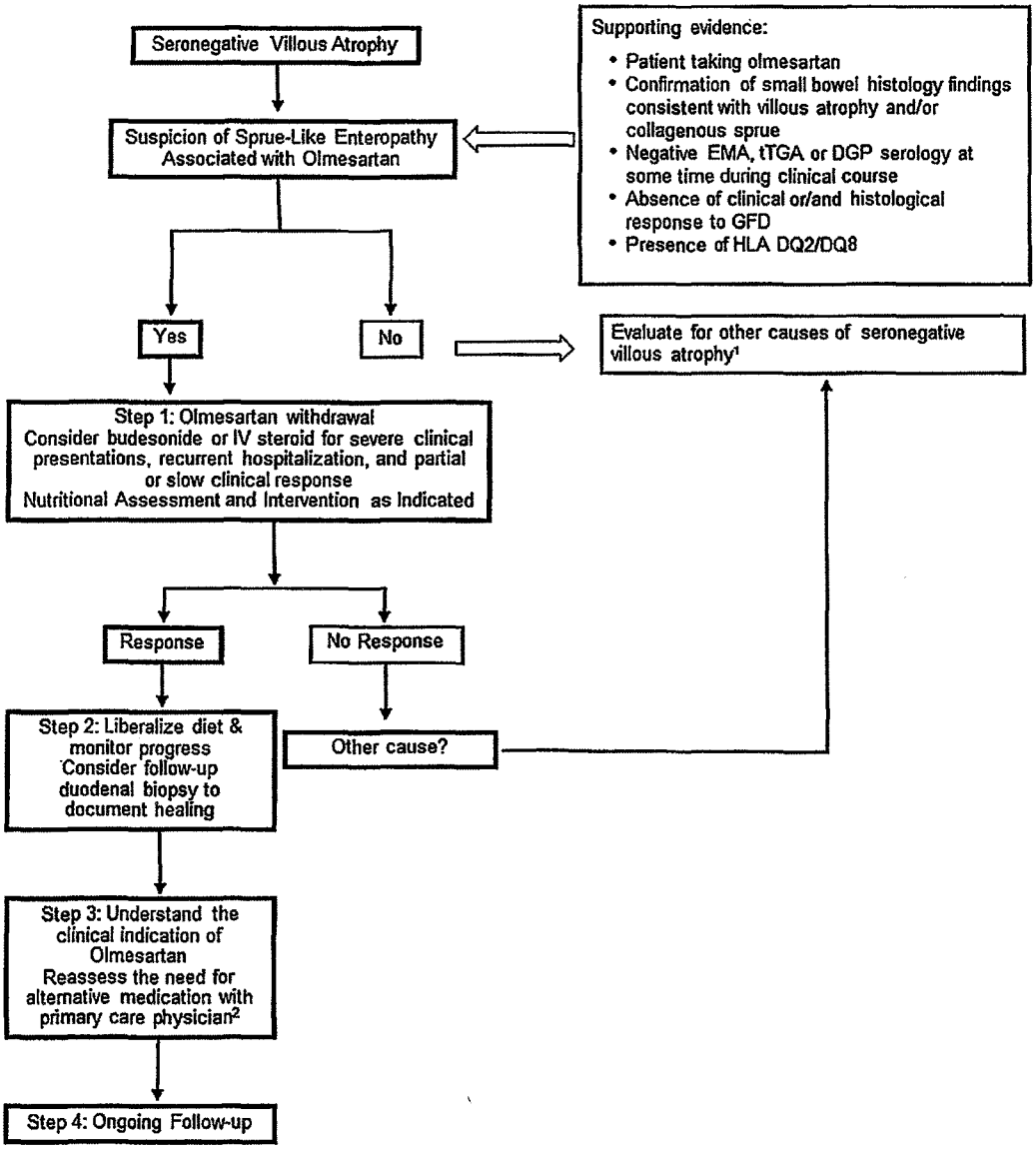

Figure 1 Proposed Management for Patients with Sprue-like Enteropathy associated with Olmesartan. 1. Differential diagnosis includes (but it is not limited to) seronegative celiac disease, other drug-related enteropathies, autoimmune enteropathy, tropical sprue, small-bowel bacterial overgrowth, hypogammaglobulinemic sprue, Giardiasis, refractory celiac disease, Whipple's disease, collagenous sprue, and unclassified sprue. 2. If there is a need for continuation of alternative therapy, we recommend to use a different class of medication whenever is clinically possible.

and cost-effective diagnosis. It is our practice that following olmesartan withdrawal, we try to understand the primary indication for olmesartan therapy and reassess the need for alternative medications together with the patient's primary care physician. It has been our experience that a considerable number of patients do not need any medications after suspension of olmesartan.

Eusébio et al.[34] identify a unique finding of elevated transaminases in a case of olmesartan associated enteropathy. They propose that this may be due to the same mechanism behind the hypertransaminasemia seen in CD.

Carneiro et al.[33] report on a case diagnosed with systemic sclerosis during the work-up for sprue-like enteropathy associated with olmesartan. The association with autoimmune diseases has been reported in several other studies.[3,5,23] In line with this observation, there are reports of individuals with sprue-like enteropathy associated with olmesartan responding to immunosuppressive treatment.[5,23] Our open-label experience suggests that some patients with severe symptoms, recurrent hospitalizations due to dehydration or both slow and/or partial response to olmesartan withdrawal may have some benefit from a short course of steroids such as budesonide (Fig. 1).

The association between autoimmune diseases and olmesartan associated enteropathy is consistent with the emerging evidence supporting an immune-based pathophysiology. One recent study by our group looking at duodenal biopsies of those taking olmesartan versus those who had discontinued the medication showed an increased CD8+ cells, FoxP3+ cells, and IL15R in biopsies of those taking olmesartan, similar to what is seen in CD.[35] In addition, we demonstrated an increased IL15 expression and disruption of tight junction proteins (ZO-1) in olmesartan-treated Caco-2 cells.[35] This suggests that olmesartan may trigger a similar change in intestinal epithelial cells as gluten does in those with CD although further study of the underlying mechanisms would be needed to fully understand the pathophysiology of sprue-like enteropathy associated with olmesartan, the new kid on the enteropathy block.

Conflict of interest

The authors declare no conflicts of interest.

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Exhibit D

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

- - -

IN RE: BENICAR (OLMESARTAN) PRODUCT LIABILITY LITIGATION	:	Civil No. 15-2606(RBK)(JS)

- - -

February 10, 2017

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PROTECTED INFORMATION

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Oral expert deposition of BENJAMIN LEBWOHL, M.D., M.S., taken pursuant to notice, was held at the law offices of Robins Kaplan LLP, 601 Lexington Avenue, Suite 3400, New York, New York, beginning at 9:45 a.m., on the above date, before Kimberly A. Cahill, a Federally Approved Registered Merit Reporter and Notary Public.

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- - -

epidemiology at Mailman School of Public Health, and so I am an epidemiologist.

Q. But you're not a biologist.

A. That's a term we don't really use so much in clinical research or epidemiological research; but if you mean colloquially the notion of someone who performs in vitro studies with pipettes and tissue cultures, that is not my day to day or -- focus.

Q. I understand.

Dr. Lebwohl, have you read any articles that indicate or suggest that olmesartan causes inflammation in the intestine of animals?

A. I am not deeply acquainted with the animal literature on olmesartan except for what I would argue is the most relevant animal, humans.

Q. So you're not familiar with the animal studies.

A. I do not have a deep familiarity with animal studies relating to olmesartan.

data to the contrary that you're aware of?

A. I'm not aware of any published studies that dispute causality. In fact, this is now an entity that's being increasingly recognized around the world.

And until I read expert reports from the defendants' side and until I started reviewing depositions, I had no idea that there were people who denied the existence of olmesartan enteropathy.

Q. Your review of defendants' reports was something that you engaged in after you wrote your report; correct?

A. To the best of my recollection, correct.

Q. Is it your opinion, Dr. Lebwohl, that all medical literature on the subject indicates that olmesartan causes sprue-like enteropathy?

A. I would say that there is no convincing published literature that puts

allergic reaction.

It suggests that there does appear to require either some sort of cumulative effect of damage or some sort of priming of the immune system or some cofactor that perhaps was not present during -- at the beginning or onset of olmesartan use, but with long enough time of exposure of olmesartan, that as yet unidentified cofactor could be triggering olmesartan's induction of enteropathy.

BY MR. MURPHY:

Q. Is it your --

A. If I could just finish.

Q. I'm sorry. I didn't know you were...

A. So celiac disease in certain ways provides an analogous situation. People with celiac disease develop symptoms, and the biologic mechanism for the symptoms in many patients is villous

atrophy and the cause of that is gluten.

And yet the onset of not just symptoms, but villous atrophy, in celiac disease can occur as young as first year of life when gluten is first introduced, but often can happen years later, even in -- even in adulthood. It doesn't mean that it was something else that was responsible for the celiac disease. It's clearly gluten that is the cause.

In epidemiology, we sometimes use the term "causal pies" when discussing causality and it's a metaphor. If you've ever played the game Trivial Pursuit, the notion that you win the game when you've filled out the entire pie, olmesartan is what is necessary for developing olmesartan enteropathy, but it might not be sufficient. There might be some other factors that need to be present.

So we don't yet know what those factors are, but one can speculate,

for example, someone taking olmesartan for years, but then has some breakdown in the gut barrier that allows olmesartan to encounter components of the immune system that it had not previously been exposed to, so a gastroenteritis or some other cofactor, and only when that happens does the patient develop olmesartan enteropathy.

This is -- this strikes me as one plausible way to explain why olmesartan doesn't cause enteropathy in everyone, but only in some individuals who have those other cofactors or who develop those cofactors over time.

Q. So is it your -- your testimony, Doctor, that, in your view, olmesartan causes sprue-like enteropathy in individuals in different ways?

A. I would say that it causes enteropathy in a subset of individuals, and the clinical manifestations and laboratory and histologic manifestations can vary.

enteropathy incident to olmesartan therapy in less than a year --

THE WITNESS: Do you mean due to olmesartan therapy?

MR. MURPHY: No. An individual who is taking olmesartan and they then present with symptoms of enteropathy.

THE WITNESS: While still taking the olmesartan regularly or intermittently or what have you?

MR. MURPHY: Yes -- in less than one year, comparing that individual to someone who does not present with enteropathy while on olmesartan therapy until two years or more, my question to you is, does the olmesartan -- in your view, does the olmesartan cause the enteropathy in the same way?

THE WITNESS: I don't think we know enough to be sure yes or no. It's very possible that there are very similar features between

those two and that the major differences between someone who presents late and someone who presents early could be related to the development of whatever that unidentified cofactor is.

But even getting beyond biology, there could be social differences. For example, someone could have the unfortunate experience -- and I've certainly seen such cases -- of a patient going from doctor to doctor, including gastroenterologists, and being misdiagnosed again and again until finally someone who was familiar with the clinical entity of olmesartan enteropathy makes the diagnosis.

Someone else who is luckier, though still unlucky because he or she has this syndrome, might get it more promptly recognized because they were in an area or in

an institution or had a provider or knew someone who was more familiar with the entity.

We have great experience in this regard in the world of celiac disease. There has been, you know, a real spectrum of duration of symptoms prior to diagnosis and this is due to another -- a number of factors; but even for celiac disease, in which gluten triggers enteropathy in the susceptible individuals, there are people who go to multiple doctors and don't get recognized, and so there's certainly a wide variation.

Sometimes these two clinical phenotypes are very similar. It's just that one person suffered for longer before she got diagnosed. Sometimes the phenotypes are different.

BY MR. MURPHY:

Q. You mentioned similarities

back of my mind and not explicitly in the fore of things when I was preparing this report, but only in subsequent review or in further discussion with Mr. Slater or in review of subsequent depositions did I realize, well, this is relevant, we should put this in.

For Padwal and colleagues, this was a study that I had minimal or very vague recollection of at the time that I wrote the report, and only when I saw that it was cited in other reports did I realize this really should be something that I should comment on or take into account.

And I can go over some others if you'd like. So --

Q. Well, let me -- I'm sorry.

A. For example --

Q. Go ahead.

A. -- let me just finish -- I believe Uehara and colleagues was a case report that I was not aware of until after I completed my report and only

there at the time that I wrote my report. I think that would be a helpful hint.

I would say I was -- Padwal and colleagues I think I gave as an example of something that really was not something that I -- was in the forefront of my recollection and I remember seeing it noted and asking myself, have I seen this, and then I had to look at it again and it sort of jogged my memory. I think that chalk that one up to search engine optimization. It's not something that mentions olmesartan in its title, so it could have been that I missed it when doing a literature review.

I think that -- I'm pretty sure that number 19, Gujral and colleagues, was an article that I was not specifically aware of at the time that I generated my report, but actually went back, because there was a statement in one of the expert reports that I thought -- that I took an issue with that suggested that it's irrelevant to study

yes, my recollection was -- was stimulated by seeing these mentioned in either expert reports or depositions.

Q. With regard to the condition sprue-like enteropathy, what are the characteristics of that syndrome?

A. Sprue-like enteropathy, are you referring to olmesartan enteropathy as sprue-like enteropathy that's been variously called sprue-like enteropathy associated with enteropathy, olmesartan enteropathy, or olmesartan-induced enteropathy? Is that what you mean?

Q. Correct.

A. There are a number of characteristics. It is a clinical diagnosis that takes into account a number of parameters on a number of different axes. There are histological features. There are clinical features and there are temporal features.

And I would say there's no one case that is the platonic ideal of olmesartan enteropathy, but there are

various features that have been reported.

Q. When you say that there are various, they vary from patient to patient; is that correct?

A. The features can vary from patient to patient, just like in a heart attack, it's reasonable, especially colloquially, to say, a heart attack, the features are chest pain. But there are plenty of people who have a heart attack or a myocardial infarction don't have that. Now, that is a clinical entity that has much more of a studied track record, so there have been formal definitions.

That's not the case in olmesartan enteropathy at this point because it's, A, new and, B, inadequately recognized and studied.

Q. Now, one thing I neglected to ask you is whether there were any deposition transcripts that you reviewed after you finished or concluded your report.

Q. -- that you want to identify for me?

A. Why don't I take a look.

Q. Please do.

A. I think the Basson paper does address the issue of causality.

Q. It reaches a conclusion regarding causality; is that what you're saying?

A. Not exactly.

Q. Or does it assume from the beginning that causality exists?

A. Let's look at how the Basson paper ends. Basson and colleagues write, "This paper shows with a higher level of evidence the association between intestinal malabsorption and olmesartan exposure"; and then a couple of sentences later, "Patients treated with olmesartan should be informed about the risk of this complication and should be advised to seek medical attention if they experience GI symptoms."

So while they do not in all

capital letters say olmesartan causes enteropathy, they certainly suggest it, because why would a group of investigators say if you're taking this medicine and you have these symptoms, you need to get this checked out if they thought that this was an association and a correlation rather than causation?

Because that's really what we're trying to tease apart when we have some people who use the word "association" and some people use the word "cause" or "induce."

Typically, the real question is, is there a third variable lurking? And if Basson and colleagues believe that a third variable were lurking, they would not be telling patients to go check this out if you're on olmesartan.

Q. I understood you to say -- and I think we understand -- that Basson, et al were looking at malabsorption; correct?

A. Basson, et al used the data

that they had available to them and they looked at codes relating to hospitalization for malabsorption --

Q. Right.

A. -- and also for celiac disease.

Q. So my question --

A. They were looking really for a surrogate for enteropathy. After all, there's no international classification of diseases code for sprue-like enteropathy induced by olmesartan. There might be in the future, but right now there isn't, and especially in the days before this was widely at least reported to be a problem with olmesartan.

This is what they had and so that's what they used.

Q. So with regard to the features of the sprue-like enteropathy, olmesartan-associated enteropathy, is malabsorption a common feature?

A. It is a clinical feature, though --

Q. I said common feature. Is it a feature that is common to all who have been diagnosed or are suspected of having that condition?

A. Malabsorption in and of itself is not necessary for sprue-like enteropathy. Malabsorption in and of itself is actually -- has been defined in different ways by different individuals.

There can be clinical malabsorption based solely on the fact that the patient reports seeing changes in one's bowel movement that looks like fat in the toilet -- and I apologize if I'm being explicit -- there is malabsorption which is declared based on the presence of deficiencies of various vitamins, and then there's malabsorption that's based on formal stool testing and other testing.

Malabsorption therefore is a somewhat broad term that's defined variously in the medical literature and in clinical practice. And so to say that

it is -- were your words commonly seen in all patients?

Q. Common to.

A. Common to all patients? Well, certainly I wouldn't know how to parse that.

Is that what he asked?

Q. I'm telling you what I asked you. So here's my next question to you.

A. I'm sorry. Can we go back to that question or is that okay?

Q. Have you answered that question?

A. I would say that malabsorption is sufficiently vague so as to not be a great way to be noted as a universal or common to all patients with olmesartan.

Q. So then am I correct that in your view, malabsorption is not a symptom that is required to diagnose sprue-like enteropathy?

A. So depending on how you consider malabsorption, but certainly

fatty diarrhea, for example, not all patients with olmesartan enteropathy reported that. One can have severe injury of the small bowel, for example, due to olmesartan and still somehow, you know, retain the capacity to absorb fat.

And, you know, you could potentially have that patient also with iron deficiency anemia and one person might actually say that is malabsorption because they are malabsorbing iron; whereas, someone else might say, I consider malabsorption to be specifically related to fat malabsorption and, if there's no diarrhea, I wouldn't call that malabsorption.

So I think it's not a very helpful term when trying to characterize a clinical phenotype --

Q. How about villous atrophy; is villous atrophy a symptom or condition that is common to all who have been diagnosed with sprue-like enteropathy?

A. I'm still getting hung up on

"common to all." I apologize, but it doesn't seem to make sense.

Q. That's fine. To diagnose someone who you believe has sprue-like enteropathy, must that individual present with villous atrophy?

A. I think that the literature has borne out that villous atrophy is not always a feature in olmesartan enteropathy; and, frankly, in real life, many patients with diarrhea don't end up even getting a duodenal biopsy.

If I could refer you to the study on my reliance list where I'm the lead author published in Gastrointestinal Endoscopy that I made passing reference to previously on sex and racial disparities in the diagnosis of celiac disease, in that study, we looked at a national endoscopy database, a clinical outcomes research initiative national endoscopy database, and we found that a large proportion of individuals undergoing endoscopy for a number of

clinical features suggestive of celiac disease, including diarrhea, iron deficiency, anemia, weight loss, who underwent endoscopy nevertheless did not have a small intestinal biopsy performed. And we thought that was remarkable and worth publishing.

And the take-away is that it appears that, in the community, people who have symptoms suggestive of malabsorption or symptoms that are certainly compatible with olmesartan enteropathy, not only might they undergo an upper endoscopy, it's possible some of them get an upper endoscopy and don't even have a biopsy.

And so I would be hesitant to say that villous atrophy is quote common to all patients who have olmesartan enteropathy, when we know that at least in an analogous disease, a lot of patients never get biopsied.

Q. Well, I guess then the question becomes, among those who in fact

have had the endoscopy, is there a finding of villous atrophy?

A. It has certainly been reported and indeed in the Rubio-Tapia initial case series, they all had villous atrophy, but as the literature has subsequently borne out, it appears that lesser degrees of villous architectural distortion or perturbation can be present.

And I think that makes sense. I'm honestly not very surprised that that was borne out based on, again, analogizing to celiac disease. Turns out that while villous atrophy is present in celiac disease, there are people who get biopsied and, due to a number of circumstances, they don't have villous atrophy in that biopsy specimen.

That could be due to the fact that villous atrophy in celiac disease is patchy and that might not be -- that might -- rather, that might be the case in olmesartan enteropathy. It

could be that it was just missed in terms of location.

Certainly one thing we've learned from celiac disease is, the small intestine does not have to look abnormal to the naked eye on endoscopy in order for a patient to have villous atrophy, and I think that's one reason for the underbiopsy rates in celiac disease. People might be assuming that if it looks okay to the naked eye, it's not worth taking a biopsy.

But even among those who do get a biopsy, there is abundant literature that shows us that celiac disease at least can be missed if an insufficient number of specimens are submitted, and there's also been a number of case reports of findings convincing for the clinical phenotype of olmesartan enteropathy in which the villous architecture was actually above what we consider normal, otherwise known as a villous height to crypt depth ratio was

seen as normal.

Q. I was asking you about features, features that are common in the diagnosis of sprue-like enteropathy. And you told me no as to malabsorption --

A. I'm sorry. I don't think that -- I believe --

MR. SLATER: Yeah, I object to the form of the question.

You can answer.

THE WITNESS: I don't think I said, no, that malabsorption -- in response to the question of malabsorption was a feature.

I just think that malabsorption is a somewhat ill-defined entity and so I'd be hesitant to say that it's common or rare within olmesartan enteropathy simply because it can be defined variously.

BY MR. MURPHY:

Q. And the same with regard to villous atrophy.

MR. SLATER: Objection.

THE WITNESS: Villous atrophy has more objective definitions than malabsorption. While interobserver agreement between pathologists is not perfect with regard to the presence of villous atrophy and I certainly have had the experience where patients with celiac disease have a biopsy that's interpreted differently by two different pathologists, there are more agreed-upon parameters for villous atrophy than there are, for example, for malabsorption.

And so, for example, if a doctor is referring a patient to me and over the phone he says that this patient has villous atrophy, I'm pretty sure I know what that doctor means; whereas, if they say malabsorption, I sort of chalk that up to a, well, that could

mean a lot of different things.

In medicine, we have such terms and I tell my trainees to be careful when using terms that are defined variously. Lethargic is another -- is another example. Lethargic could mean somewhat sleepy because of insufficient amount of sleep. Lethargic could mean substantial mental status change and we need to work this up acutely because we're worried there's something going on.

Malabsorption's not quite that bad, but it's something that I think we need to exercise some caution on, particularly when trying to pin a clinical entity and label with malabsorption.

BY MR. MURPHY:

Q. How about diarrhea; is diarrhea a feature that must be seen in order to diagnose one as having olmesartan-associated enteropathy?

A. I don't think it must be present. I think that diarrhea is commonly reported in people who turn out to have olmesartan enteropathy.

Not to get too technical, there are definitions of diarrhea and there is a little bit of subjectivity to that, but I think the literature's borne out that you don't need to have diarrhea to have olmesartan enteropathy.

I believe you could have potentially constipation. I think there's potentially an explanation for that. If you have, you know, a -- an injured gut epithelium, that could potentially affect the enteric nervous system and that could actually paradoxically induce constipation. Just like, you know, some people when they're undergoing stress gain weight and some people when they're undergoing stress lose weight, there does appear to be this varied clinical presentation.

But I would say that

diarrhea is a common feature in patients with olmesartan enteropathy.

Q. With regard to constipation, did any of the -- those who were participants in the Rubio-Tapia case series present with constipation?

A. Rubio-Tapia's case series was somewhat narrowly defined. If you look at their inclusion criteria, patients were considered for inclusion of the study if they had chronic diarrhea, so it's very possible that Dr. Rubio-Tapia and colleagues were encountering other people, patients, who had olmesartan enteropathy, but they just didn't make it into this series, because they predefined who made it in.

So while it is possible to have both chronic diarrhea and intermittent bouts of constipation, it appears based on my interpretation of this paper that they were limiting their case series to those with chronic diarrhea.

"Severe Spruelike Enteropathy Associated with Olmesartan"? No, that was not a case-control study.

I believe there's one on my list, though, that you haven't mentioned, but maybe --

Q. Which -- you tell me. I thought I covered them all --

A. Greywoode?

Q. Okay. Greywoode.

A. Yeah, if I'm remembering accurately, when we resumed from the break, I mentioned two more and Greywoode was one of those two and the other was Cartee. Greywoode is a case-control study. Cartee is not.

Q. So Greywoode being a case-control study, anything in Greywoode suggest a statistically significant correlation between olmesartan and sprue-like enteropathy?

A. Well, certainly in the -- in the conclusion of our study, we make reference to the fact that olmesartan

causes severe enteropathy; but in terms of the analysis, we actually did in that study -- there were no statistically significant associations found between olmesartan and diarrhea or sprue-like enteropathy.

Q. Okay.

A. I would note, though, as we do in our study, that we really didn't have that many people taking olmesartan which severely impacted our power.

If you look, for example, at table 1, if you add up the columns of olmesartan users among those undergoing EGD, which is esophagogastroduodenoscopy, and olmesartan users among those undergoing colonoscopy, you barely get a hundred patients.

We did not know that olmesartan was going to be so unpopular at the time that we designed this study, but at the end of the day, this is what we found among these individuals in their records.

The reason that's relevant is that the fewer patients you have with regard to the exposure, the more limited one's power is and the wider one's confidence interval is.

And so, you know, as we acknowledge in our limitations section of the paper, it was also a relatively small prevalence of use of olmesartan, .7 percent to 1 percent among study patients, limiting the power of this analysis, as I say.

I would also point out the 95 percent confidence interval for olmesartan -- you can see in table 3, the odds ratio is calculated 1.99 and the 95 percent confidence interval overlaps with 1, which is the unity in terms of a signal being detected with regard to an association, and that's why the P value is 0.14, not statistically significant.

But if you look -- and this is really a direct consequence of having so few patients on olmesartan in the

to turn to page 5 of your report, please.

A. I'm on page 5.

Q. Okay.

And toward the -- about the bottom third of the page, there is a sentence that begins, "There is not a single."

A. I see it.

Q. And the sentence reads, "There is not a single invariable presentation for this condition, and the condition is ultimately diagnosed based on the clinical presentation and course, with particular attention to positive dechallenge or rechallenge."

Did I read that right?

A. Yes, you did.

Q. Is it necessary to have rechallenge to establish that olmesartan is the cause of sprue-like enteropathy?

A. Can you repeat that question?

Q. Sure. Is it necessary to have rechallenge to establish

definitively that olmesartan is the cause of sprue-like enteropathy?

A. No. Rechallenge certainly is something that we pay particular attention to and can be compelling, but it's not a -- it's not a necessary component.

Q. Is it necessary to have dechallenge to establish definitively that olmesartan has caused sprue-like enteropathy in a patient?

A. I think that if the question is to establish to a reasonable degree of medical certainty, I don't think that dechallenge is always necessary; but, unfortunately, someone could be taking olmesartan, become so ill that the patient actually dies before the olmesartan is withdrawn and sufficient evidence can make it, to a reasonable degree of medical certainty, that it was in fact the olmesartan that was causing the enteropathy.

Q. Short of a patient's demise,

is it necessary to have dechallenge?

A. I suppose that there are patients who could be lost to follow-up and for whom we don't have definitive dechallenge data, but still be very suspicious that these patients have olmesartan enteropathy, in fact, suspicious to a reasonable degree of medical certainty.

Q. What is involved in dechallenge; that is, does it require total clinical and histologic resolution?

A. No. Dechallenge involves withdrawal of the offending agent and it involves a change in those various parameters for the better, though there's not a definitive parameter that is essential.

For example, if you have someone who has a dechallenge after years of so-called refractory celiac disease, has been gluten-free, not getting better at all, and then goes off Benicar and has significant improvement, even without

Q. Now, with regard to the definitive dechallenge, to use your term --

A. I -- if I may interrupt, I'm not sure if we mean the same thing by that, but if I can define -- or why don't you --

Q. And that's what I'm asking you to do, is to define what an effective dechallenge entails.

A. If a patient is no longer taking olmesartan and there is improvement of any of -- of those parameters that make up the clinical phenotype of olmesartan enteropathy.

Q. And is there a time course for this dechallenge period where the patient gets better, so to speak?

A. It's hard to be too dogmatic about a cutoff. Of course, people take olmesartan in discrete doses. It's typically taken as a once-daily -- once-daily medication; and between those doses, one does -- even if one is not

literature --

Q. I didn't ask -- that was just a predicate to my question.

A. Go on.

Q. Okay. Your point here is that sprue-like enteropathy is often misdiagnosed as celiac disease; correct?

A. It is often misdiagnosed early on as celiac disease.

Q. And we touched on this earlier, but I want to make sure that we're clear: With regard to the subject of the 2012 Rubio-Tapia paper, certain of those individuals were misdiagnosed as having celiac disease; correct?

A. It appears that the primary reason they were being cared for by this group, in fact, was that there was a frequent misdiagnosis of celiac disease and that the initial impression had been celiac disease.

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(Deposition Exhibit No. Lebwohl-8, 2014 Paper "Sprue-like

A. I believe there might have been some overlap, but they were not identical lists of patients, that's right.

Q. And we also saw that in the Cartee and Murray paper, the authors stated that most, but not all, of the patients improved with drug withdrawal; correct?

MR. SLATER: Objection.

You can answer.

THE WITNESS: It does say that most, but not all, patients improved with drug withdrawal.

BY MR. MURPHY:

Q. Doctor, are you aware of any studies that show that increasing doses of olmesartan leads to a higher risk of sprue-like enteropathy?

A. If you're referring to dose in terms of milligram strength, I've not seen such data. Cumulative dose, as better defined as duration, does seem to indicate that.

It's my belief, though, that if one had to compare 40 milligrams to 20 milligrams, for instance, we haven't seen that traditional sort of dose-response, but I would point out that this might be the case -- and I believe this is the case -- that that is because the minimal threshold for causing olmesartan enteropathy has been far exceeded in both of those cases.

And so we don't know what that minimal threshold is, but it's probably far below the traditionally lower dose given to adults at least who are prescribed olmesartan, which was -- is typically 20 milligrams.

Q. So it's your opinion that the dose necessary to trigger or cause enteropathy is less than the 20 milligram dose?

A. I suspect that people with olmesartan enteropathy have that enteropathy triggered or would have that enteropathy triggered by less than 20

milligrams simply because it appears that we don't see that higher milligram dosages of enteropathy within the traditionally prescribed dosing parameters for adults shows that kind of response.

And so I would not at all be surprised if an individual with known olmesartan enteropathy, if that individual were exposed to a lower amount of olmesartan, if that -- I would be surprised if that did not also cause enteropathy.

And certainly in clinical practice, if a patient with known olmesartan enteropathy approached me and asked if it were safe to take, for example, a half dose of olmesartan, I would say stay away from that medication entirely.

Q. With regard to dose-response -- and I'm not talking about the long-term temporal aspect of dosage, but dose-response -- my question to you was

whether there are any studies showing an increase -- that increased dosage of olmesartan leads to a higher risk of sprue-like enteropathy.

A. It appears that the threshold for inducing sprue-like enteropathy is well below the traditionally prescribed lowest dose of olmesartan enteropathy; and so to my knowledge, the typical doses that are studied are within that traditional dosing and we've not seen a dose-response within that traditional dosing.

Q. Now, what you've referred to essentially is the dose-response gradient in the Bradford Hill analysis; correct?

A. Dose-response is a component of Bradford Hill criteria, if that's what you're referring to.

Q. Indeed. If I can direct your attention to page 28 of your report, that is where you -- in that first full paragraph, where you initially address the Bradford Hill criteria for causality;

ROADMAP data, are you not?

A. ROADMAP is an acronym for a clinical trial of olmesartan, if that's what you're referring to.

Q. I am. That data was null for intestinal-related adverse events; correct?

MR. SLATER: Objection.

You can answer.

THE WITNESS: ROADMAP to my knowledge was not designed to measure intestinal adverse events.

BY MR. MURPHY:

Q. Are you not able to answer the question? My question simply was whether it was null for intestinal-related adverse events.

MR. SLATER: Objection.

You can answer.

THE WITNESS: You might be referring to a secondary analysis that was published in the Mayo Clinic Proceedings as a letter to the editor in response or after

argumentative about what I said or how I said it.

MR. SLATER: I think it is, because it's like the third time now he's explaining in very clear terms his answer, which is denying the premise of your question in very direct and clear terms.

MR. MURPHY: Adam, don't testify.

MR. SLATER: Trust me, do you think he needs me to testify?

MR. MURPHY: No, he does not. That's the point.

MR. SLATER: I'm not testifying. I'm just trying to get him to dinner, although I guess it doesn't matter what happens. The time runs no matter what so...

BY MR. MURPHY:

Q. There were, Doctor, two studies conducted at Columbia University that were the subject of papers in which

prednisone or budesonide or whatever it was. If anything, it was a transient response, because after all, they all relapsed after, so I certainly wouldn't characterize that as 100 response or 100 percent response.

Q. But majority; correct?

A. I think --

Q. You would agree with majority.

A. I think it's the same issue, that all of these patients had some degree of response, but it's not clear that they had a large response. It just -- it just characterizes that they had a clinical response, which in and of itself, by the way, is somewhat subjective. It depends a little bit on what parameter one's measuring, on what the patient's reporting, and when he or she is reporting it.

And it's very possible for two groups of investigators to be encountering the same emerging clinical

condition, but to characterize either the presence or absence of a response or the degree of response somewhat differently and particularly in the absence of some sort of disease assessment score.

Q. Was there a response noted to immunosuppression in the Rubio-Tapia paper?

A. When you refer to the Rubio-Tapia paper --

Q. 2012.

A. Okay. Just wanted to make sure we're on the same page.

Their inclusion criterion seem to preclude much of a response. For example, if you look on page 733, they actually excluded a patient from their series because they improved clinically and histologically with oral budesonide before suspension of olmesartan.

That kind of patient might have made it into our series depending on the ultimate outcome with regard to whether that response was durable,

But this condition that's been variously termed sprue-like enteropathy associated with olmesartan, olmesartan enteropathy, olmesartan-induced enteropathy, yes, I believe that is caused by olmesartan.

Were you asking about clinical features?

Q. Yes.

A. I believe I answered earlier in the day that there are a number of both signs and symptoms across a spectrum of several different axes, including clinical, histopathological, and other signs in terms of laboratory abnormalities.

There's no one uniform set of strict criteria that's been developed and there does appear to be a spectrum of abnormalities on all of these axes.

How are we doing on time?

Q. You're fine.

MR. SLATER: Do you want to take a break?

105 taking olmesartan in this whole study and we now know that given the relative rarity of olmesartan enteropathy, one cannot rule out an association based on 105 patients taking olmesartan, particularly outpatients.

Q. And when you refer to milder presentations, what are you actually talking about when you refer to, again, milder presentations?

A. So I'm referring to the kind of presentation that would be sufficiently mild so as to have a patient undergo this kind of procedure.

But I would add that we actually didn't know a huge amount about this in terms of what their actual symptoms were. All we knew based on this study was, were they outpatients, why were they having their endoscopy, and what was their age/gender, and what were they taking.

I would also point out, you know, this was published in 2014 and I'm

features.

A. It has been reported among patients with evidence of olmesartan enteropathy. I would say that based on what we know today, I believe that diarrhea is more common than constipation, but constipation can be a feature.

Q. Constipation can be a feature. Diarrhea can be a feature; correct?

A. Yes, both could be features of olmesartan enteropathy, though we have more reports and experience with diarrhea as a feature.

Q. How about vomiting?

A. Vomiting has been reported as a feature of olmesartan enteropathy. That is not a necessary feature, but it certainly been reported in adverse event reports or in case reports or case series.

Q. Are there any features that you would characterize as necessary

features?

A. Yes.

Q. Which of them are necessary?

A. Exposure to olmesartan.

Q. Anything else?

A. I think it's hard to be black and white about a prototypical clinical scenario right now. There appears to be a spectrum, both histologically and clinically.

And so while there are certain features that have been reported commonly in patients with olmesartan enteropathy, like diarrhea, like weight loss, that seems to be particularly common, there are also patients who have neither of those who end up having olmesartan enteropathy. Vomiting is another such example.

But really none of them is absolutely necessary for the development of olmesartan enteropathy.

Q. With regard to this patient that is discussed in the Talbot paper,

study that I just referenced. And we're talking about clinical symptoms, not necessarily other abnormalities, whether it be laboratory or histologic.

And, again, analogy's helpful in this regard. So in celiac disease, if you take a patient with severe symptoms who's eating gluten and you diagnose him successfully and you start a gluten-free diet, in the context of appropriately elevated celiac disease serologies, often clinical improvement well predates improvement of histology, which can sometimes take years, or serology, which has, again, a more variable -- a more variable time course with regard to improvement or resolution.

And I've observed a similar clinical variability with olmesartan.

Q. So the clinical manifestation of getting better is not necessarily proof that the histologic changes have occurred.

A. A clinical response does not

correlate with a histologic response, if that's what you're asking. That's certainly the case in celiac disease.

And I think we have less histologic data upon which we rely on the olmesartan story, but I believe that the situation is analogous, that you can potentially have a difference between how a patient is doing clinically when dechallenged and how they're doing histologically.

Now, the scientist in me wants to know that answer very well and wants to study this more, but as a patient who cares -- as a physician who cares for patients, the patient cares most about clinical response; and when you have a patient in front of you who's so much better off olmesartan, it is not always clinically so relevant to the patient how they are doing histologically.

Q. But to the extent that there is a rechallenge attempted, is it not

more limited data or circumscribed data, but the process of formulating a differential diagnosis and then concluding the probability that there was a causal relationship, that's a similar process. It's just that the inputs may vary.

Q. Is it your understanding, Doctor, that the MedWatch reports that you've seen in this litigation were -- that is, the causation assessments made in those MedWatch reports -- were done pursuant to a differential diagnosis?

A. They were done pursuant to the available data that was there at the time. Now, a differential diagnosis is a process that's very commonly employed when attempting to assess for causality because one has to keep in mind what the alternatives are.

Now, if someone had reviewed this and said, you know, I think the alternative is X, Y, or Z, they would not be characterizing the causal relationship

between a suspected drug and the event as definite, because implicitly, a differential diagnosis suggests an alternative as a more plausible cause.

Q. In this MedWatch report that we're looking at here, Exhibit 13, is there any mention or evidence of a biopsy having been taken?

(Pause.)

THE WITNESS: Based on what's written in this MedWatch report, I do not see a report of a biopsy having been performed.

MR. SLATER: We gotta take a break for about three minutes. I just got an e-mail. I gotta call someone back. This will probably be maybe our last break before he finishes, but I gotta take three minutes.

THE WITNESS: All right.

(A recess was taken from 5:09 p.m. to 5:14 p.m.)

BY MR. MURPHY:

After all, as you likely know, it's an antiarrhythmic and especially when someone's acutely ill, stopping the antiarrhythmic is not something that's generally done. Particularly if one's atrial fibrillation is intermittent, times of stress can worsen atrial fibrillation.

So while it's not explicitly pointed out here, in every MedWatch report you're never going to get the entire story. There are going to be situations where if you had the patient in front of you, you might for various reasons ask for clarifications, but I have no indication here that it would be plausible that the propafenone were stopped at exactly the same time that the olmesartan was stopped and introduced at the same time that the olmesartan were reintroduced.

I think Occam's razor and general common sense would indicate that the propafenone is what we call a red

herring in this case.

Q. That's your read of the document, but the document is silent on that question of when the propafenone was discontinued; correct?

MR. SLATER: Objection.

MR. MURPHY: Or whether it was discontinued; correct?

MR. SLATER: Objection.

THE WITNESS: The document mentions propafenone but does not make any mention of any change in the propafenone, and so my interpretation is that this was not modulated in perfect congruence with the olmesartan.

Why would someone generate a report where both medicines were stopped at the same time and one is only mentioning one in terms of its starting and stopping and then mentioned as the patient was taking the other medication when, in fact, they were started and

stopped at the same time? That doesn't seem to make any sense.

I see that propafenone is mentioned and I have no reason to doubt that he had been on propafenone during this time, but I have no evidence to think that someone would only selectively report the dechallenge and rechallenge data regarding olmesartan and totally leave out any relevant propafenone dose changes.

BY MR. MURPHY:

Q. Assuming that they had that information; correct?

A. What I would say is that --

Q. Assuming that they had that information; correct?

A. They of course had information on propafenone, but they did not -- they did not -- the fact that they did not comment on its temporality and the fact that they had access to this

enteropathy in that scenario.

Q. Is it your testimony, Dr. Lebwohl, that he testified based upon a differential diagnosis that he conducted? Is that your testimony?

A. I don't see him using the words in that -- in that specific instance, but Tina Ho, for example, mentioned that when they're looking at -- and I quote -- when they're looking at the known characteristics of a subject's clinical state, that's differential diagnosis, and later says there's actually definitions of related and not related which, again, just lumps in the different clinical criteria that the medical reviewer would be applying in doing a differential and exercising medical judgment.

And so a differential diagnosis can certainly be applied when reviewing a MedWatch case report.

Q. And my question simply to you is whether you were stating that Dr.

vomiting, diarrhea, and weight loss about one year after starting Benicar HCT; correct?

A. Give me a moment just to refresh my memory looking at this MedWatch report again.

Q. I'm just asking whether that's what you say in your report.

A. That's what I write in my report, yeah.

Q. Okay.

(Pause.)

THE WITNESS: Okay. Do you have questions?

MR. MURPHY: Yes, I do.

BY MR. MURPHY:

Q. Again, you indicate that the patient experienced weight loss, severe vomiting, and diarrhea while being treated with Benicar; correct?

A. That's what I wrote.

Q. And, in fact, the patient -- it's reported that the patient started Benicar a year before his symptoms, while

also intentionally dieting, attempting to lose weight; correct?

A. It does say that he was intentionally dieting; and despite that and even though weight loss is the goal of intentional dieting, the fact that he's reporting weight loss in my opinion doesn't undercut the notion that he's been dieting.

In medicine, we like to say that a successful diet is a disease until proven otherwise. It's very possible that he was trying to lose weight and was unsuccessful and then when he started developing these other severe symptoms, then he was tragically successful in his weight loss or perhaps the weight loss accelerated.

MR. SLATER: One second. He just answered quickly. I just object to the foundation of the question. I didn't want interrupt him. I didn't want to object when he was speaking, but I just wanted

you to know that because there's a flaw there.

BY MR. MURPHY:

Q. And in this MedWatch form, Exhibit 16 that we're looking at, is there any evidence of a biopsy having been taken?

A. I suspect a biopsy was done --

Q. No, my question is --

A. -- I cannot point you to --

Q. -- it indicated or reflected in the document? That's my question to you.

A. Biopsy, the word, was not used, but there is a pair of important words that strongly suggest a biopsy was done and I believe the biopsy was done in this case. The word is celiac disease. It says concomitant diseases, celiac disease. Celiac disease is triggered by gluten and is diagnosed based on biopsy. The fact that one is going on record with a diagnosis of celiac disease to me

strongly suggests that a biopsy was done.

In fact, this -- if all I knew was that this was a 35-year-old man with celiac disease, who's black, I would immediately start to wonder about alternative explanations for so-called celiac disease and question if it's a misdiagnosis.

We know that people who self-define as having black race have much less celiac disease in terms of their prevalence; and while it's certainly possible -- and I have a handful of patients with celiac disease who self-identifies African-American -- I also have -- I can remember at least one black patient who was told she had celiac disease, but, in fact, on further workup, had olmesartan enteropathy. And so this to me immediately raises concern. And then -- that's not even seeing that he was on olmesartan yet.

And then I see he was on olmesartan and he had a positive

rechallenge in the context of two positive dechallenges. This to me is illustrative of the kind of cases that exemplify olmesartan enteropathy.

Q. Doctor, at page 36 of your report --

A. I'm on page 36.

Q. -- at the bottom, toward the bottom of the page, four lines up, you begin a sentence "Another example"? Do you see that?

A. I see it.

Q. "Another example is a MedWatch documenting an adverse event reported to Daiichi Sankyo on September 15, 2005, with regard to a 58 year old female patient who took Benicar for two years."

A. I see that.

MR. MURPHY: I'm going to mark as Exhibit 17 the MedWatch report that you reference.

- - -

(Deposition Exhibit No.

the finding, do you have an opinion, and if you can explain this, as to why that is an important article in the overall question of causation and how it fits into the determination that you've given of causation?

A. A specific aspect of the --

Q. You know what, I'm going to withdraw that question, actually. I want to ask you about something else, actually. I want to ask you a completely different question, actually.

A. Okay.

Q. I think you handled that one for about an hour. I'm not going to go back into it.

Here's my question: You were asked about the so-called hierarchy of different types of studies, RCTs, all those other type studies; and in the context of olmesartan, in identifying and studying the entity of olmesartan enteropathy, can you just give us an explanation of why it is or what your

opinion is as to which studies have been most helpful in understanding that entity in the literature?

MR. MURPHY: Objection to form.

You may answer.

THE WITNESS: In fact, it's the case reports with multiple dechallenge and rechallenge in multiple contexts from around the world that are actually most helpful.

There are other study types that we talked about earlier today that have added to the impression, but convincing case reports with well-documented dechallenge and rechallenge data can be the most helpful, despite the fact that in a generic pyramid of evidence, case reports are on the bottom.

In fact, RCTs are not well suited to look at uncommon long-term effects, both because

the number of patients in an RCT, for example, the ROADMAP study, is not sufficiently high so as to look for an uncommon effect, nor do they follow patients long enough to look for a long-term adverse effect.

And I should add that even within the ROADMAP study, it turned out that there were patients who had olmesartan enteropathy which was not noted by the authors of that post hoc analysis.

BY MR. SLATER:

Q. And when you say there were patients that were noted that had that, was that based on your review of internal documents that were not publicly shared with the medical community?

A. Yes.

MR. MURPHY: Objection to form.

BY MR. SLATER:

Q. So does that confirm for you that there was a lack of follow-up data on that one patient?

A. Correct.

Q. With regard to the Bradford Hill criteria, did you consider the nine different criteria as you evaluated the evidence that was available to you in forming your opinions in this case?

A. I considered those criteria when I was evaluating the evidence.

Q. Even though you may not have specifically named a few of them, it's your testimony you did consider the entire criteria?

A. Correct.

Q. And I think you mentioned a few of the criteria during the course of your testimony, like cessation of exposure and others, those were criteria you were aware of and applied?

A. Yes.

Q. In the Greywoode article, there is a statement in the article

suggesting that milder presentations are unlikely at that time. That's part of the conclusion in the abstract?

A. Yes, it is.

Q. What's your opinion now at this time and at the time you wrote your report in this case as to whether it is likely or unlikely that there are milder presentations of olmesartan enteropathy?

MR. MURPHY: Objection; form.

You may answer.

THE WITNESS: I believe that milder presentations are, in fact, likely.

BY MR. SLATER:

Q. Is that in part based upon review of the literature and the case reports that have been coming out even up till very recent?

A. Correct.

Q. You were asked about internal company documents. And do you and other physicians in the medical

Exhibit E

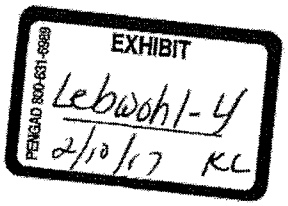
UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION	MDL No. 2606
THIS DOCUMENT RELATES TO ALL CASES	HON. ROBERT B. KUGLER

RULE 26 EXPERT REPORT OF BENJAMIN LEBWOHL REGARDING GENERAL CAUSATION

I have reviewed the documents, materials and literature identified in this report and the Appendices, including the reliance list set forth at Appendix 1. Based upon the analysis of these documents and materials, as well as my knowledge, experience, and training, and knowledge of the applicable literature, set forth herein and in my Curriculum Vitae attached as Appendix 2, I have formed opinions with regard to the question of whether Olmesartan Medoxomil causes sprue-like enteropathy and related gastrointestinal effects in a subset of users of the medication (referred to as "olmesartan enteropathy" herein). In evaluating and answering this question, I apply accepted scientific methodology, relying on the peer reviewed medical literature, and the process whereby olmesartan enteropathy has been identified and diagnosed in patients. Each of the opinions set forth is held to a reasonable degree of medical certainty.

SUMMARY OF QUALIFICATIONS AND EXPERIENCE



I am a board certified adult gastroenterologist based at the Celiac Disease Center at Columbia University, a major referral center for patients with celiac disease and related disorders. My current academic appointment is Assistant Professor of Medicine and Epidemiology. I joined the faculty of the Center in 2010 after completing a residency in internal medicine at Columbia and a fellowship in digestive and liver diseases, also at Columbia. My course of training included three years of training in internal medicine followed by an extra (optional) year as a chief medical resident, which consisted of teaching, administration, and leadership in the department of medicine, followed by three years of gastroenterology fellowship, which consisted of training in the clinical care of individuals with digestive and liver disease. This included exposure to inpatient and outpatient conditions, history and physical examination skills, medical decision making, and the performance of gastrointestinal procedures including esophagogastroduodenoscopy and colonoscopy. In addition to my clinical and academic appointments and work, I am on the Editorial Boards of Clinical and Translational Gastroenterology and Digestive Diseases and Sciences, and I serve as a peer reviewer for multiple journals, including but not limited to the New England Journal of Medicine, JAMA, Gastroenterology, and Gut. I have significant research interests, and I have co-authored 88 original research publications in the peer reviewed literature, along with numerous other academic publications.

During my three-year fellowship at Columbia I concurrently obtained a master's degree in Patient Oriented Research from the Department of Biostatistics at the Mailman School of Public Health, also at Columbia. While I was a student at the Mailman School I completed coursework in epidemiology and established research collaborations with investigators in the

Department of Epidemiology that continued after I completed my training. In 2011 I joined the faculty of the Department of Epidemiology at the school. My activities in the Department of Epidemiology have included advising master's students, serving as a research mentor for epidemiological research projects, lecturing to epidemiology students, and participating in the composition and grading of the written examination for PhD candidates in epidemiology. Although my primary area of training is in clinical gastroenterology, I have been invited to adjudicate in the dissertations by epidemiology PhD candidates both within my institution (Columbia) and outside institutions (University of Umea, Sweden and University of Calgary). I am being compensated for my time at a rate of $550/hour or $5000/full day in court or in a deposition. I have not previously testified in court and have been deposed once in December 2012 as an expert witness in a medical malpractice case. The case name was Sepe v. London.

OVERVIEW

Olmesartan Medoxomil, the active ingredient in the Benicar family of products (Benicar, Benicar HCT, Azor, Tribenzor, collectively referred to herein as "Benicar" and "olmesartan"), is indicated for the treatment of hypertension. Benicar is manufactured and sold by Daiichi Sankyo, and is within the class of anti-hypertensive medications known as Angiotensin II Receptor Blockers ("ARB's"). Benicar (the trade name) was first approved and marketed in the United States beginning in 2002, and then in Europe in 2003. Marthey, et al., Olmesartan-associated enteropathy: results of a national survey. Aliment Pharmacol Ther 2014; 40:1103-1109. There are many drugs on the market for the treatment of hypertension, including the other ARB's, angiotensin converting enzyme (ACE) inhibitors, and other medications and combinations of

medications are utilized as well. At all times starting with the initial marketing of Benicar there have been numerous safe and effective medications available for the treatment of hypertension, aside from Benicar.

The development process for Benicar is described in the deposition of Donald Hinman. Benicar's mechanism of action for the treatment of hypertenstion is linked to the small intestine, the location for activation of the pro-drug, olmesartan, with most absorption in the small intestine. (Donald Hinman, 81:8-22). The development history, structure, metabolism, and other technical background of olmesartan is summarized in a recent publication. Marietta, et al. Drug-Induced Enteropathy. Digestive Diseases 2015;33:215-220. Of note, the pre-clinical and clinical testing that was performed was not adequately powered or designed to study gastrointestinal adverse effects. No specific test or study was performed prior to marketing Benicar to determine whether there was any effect on the gastrointestinal system, and there was no clinical or preclinical study performed to determine whether olmesartan, "caused any changes to the villi in the intestine, the small intestine." (Donald Hinman, 29:14-22, 48:7-16). The lack of any study of potential gastrointestinal side effects prior to marketing Benicar is consistent with the fact that Benicar was not designed to have any impacts on the gastrointestinal system, and was not expected to cause sprue-like enteropathy, or a syndrome or constellation of symptoms that would present like celiac disease. (Allen Feldman, 69-70). The label for Benicar referenced diarrhea, seen in clinical studies, no greater than placebo, but this was not meant to describe a risk of chronic diarrhea. (Allen Feldman, 72). Of interest, Mr. Hinman testified that Daiichi Sankyo does not fully understand, "the entire process whereby the drug is absorbed, metabolized and acts within the

body...The full extent of the mechanism of action is not fully understood." (Donald Hinman, 128:8-130:5).

It is now firmly established in the medical literature that a subset of patients utilizing Benicar develop a gastrointestinal syndrome characterized as sprue-like enteropathy, with related gastrointestinal side effects as a result of using this medication. This condition is referenced internally by Daiichi Sankyo as olmesartan associated enteropathy, and olmesartan induced enteropathy, meaning that the enteropathy is caused by olmesartan. (Allen Feldman, 356:11-15) As set forth above, I refer to this condition as olmesartan enteropathy. This condition is characterized by delayed onset duration, generally with an onset in the range of months or (more often) years. The resulting clinical syndrome typically manifests with dehydration and other malabsorptive symptoms such as severe chronic diarrhea and/or vomiting, significant weight loss, abdominal pain, nausea, and related systemic effects. Where intestinal evaluation and biopsies are performed, the specimens generally demonstrate inflammatory changes including partial or total villous atrophy. Findings can include increased intraepithelial lymphocytes and microscopic colitis, among others. There is not a single invariable presentation for this condition, and the condition is ultimately diagnosed based on the clinical presentation and course, with particular attention to positive dechallenge or rechallenge. The findings on pathology can be useful in ruling out potential causes, and for correlation with the clinical presentation and course. Deposition testimony indicates that an internal Daiichi Sankyo document recognizes that where villous atrophy is identified this should be understood to be due to organic change in the small intestine, as opposed to a functional change such as with ordinary diarrhea. (Hideki Tagawa, 83:19-84:8). This condition has been misdiagnosed, most often as celiac disease in many patients, or other

inflammatory disorders due to the similar clinical presentations, and a lack of knowledge about olmesartan enteropathy in the medical community. Burbure, et al. Olmesartan-associated sprue-like enteropathy: a systematic review with emphasis on histopathology. Human Pathology (2016) 50, 127-134.

I first learned of an association between olmesartan and a sprue-like enteropathy in April 2012. My colleague Peter Green, founder and director of the Celiac Disease Center at Columbia University, mentioned a conversation he had with Joseph Murray, a celiac disease expert at the Mayo Clinic, about his findings that a number of patients thought to have refractory celiac disease or collagenous sprue had been taking olmesartan, and that their symptoms and histology resolved after discontinuation of the drug. At the time, this condition had not appeared in the medical literature, aside from a passing mention of olmesartan in Dr. Murray's 2010 publication on collagenous sprue. Rubio-Tapia, et al. Gluten-Free Diet and Steroid Treatment Are Effective Therapy for Most Patients with Collagenous Sprue. Clinical Gastroenterology and Hepatology 2010; 8:344-349. Upon hearing about this from Dr. Green, my colleagues and I reviewed the charts of our most treatment-resistant patients, and were struck by the fact that olmesartan was a common feature. I reached out to a number of patients at that time, informing them of this possible association, and advising them to discontinue the drug. This resulted in some of the most dramatic clinical improvements I have witnessed as a physician. To this day, some of my most grateful patients are those who went from being desperately ill, with weight loss and severe diarrhea necessitating multiple hospitalizations, to total clinical and histologic resolution after discontinuing olmesartan. Typically these are patients who have first been evaluated and treated (by me or others) with invasive procedures, and ineffective or transiently effective modalities

including a gluten-free diet, an elimination diet (involving extraordinary efforts to minimize cross-contamination by gluten), corticosteroids, and immunomodulators, prior to olmesartan being identified as the culprit.

By the time Dr. Murray's group published its series of 22 patients (Rubio-Tapia, et al. Severe spruelike enteropathy associated with olmesartan. Mayo Clin Proc. August 2012;87(8):732-738) in August 2012, my colleagues and I at the Celiac Disease Center at Columbia had a number of patients whom we diagnosed with this condition. By that time, I had started reintroducing dietary gluten to these patients and found that they remained healthy when doing so. We realized that patients with olmesartan enteropathy were being misdiagnosed as having celiac disease, given that these two conditions have similar histologic features. In addition, during this time, I was participating in a study evaluating our Center's experience of seronegative villous atrophy, the term used to describe the existence of duodenal villous atrophy with the absence of abnormally elevated celiac disease antibodies (tissue transglutaminase antibodies and deamidated gliadin peptide antibodies). Given the information we had received from Dr. Murray and our own experience of dechallenged patients who then improved, we reviewed the records that we had collected and found that, of 72 patients with seronegative villous atrophy, 16 (22%) were ultimately attributed to olmesartan use. Though we had not initially set out to study olmesartan in that paper, we found that olmesartan was the most common agent in those diagnosed with medication-related villous atrophy. DeGaetani, et al. Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma. Am J Gastroenterol 2013;108:647-653.

Despite the Mayo Clinic publication in 2012, the subsequent publication of our series corroborating Dr. Murray's experience, as well as additional case reports, and despite the label change on July 3, 2103, and the July 3, 2013 Safety Notification by the FDA stating that olmesartan can cause sprue-like enteropathy, I continued to see patients with severe malabsorption who, while taking olmesartan, were evaluated by one or more previous gastroenterologists and were told that they had refractory celiac disease. As a result of my knowledge of this condition, I adopted a practice where, when a referring colleague calls me, asking me to see a sick and complicated outpatient on short notice as a second opinion, I will first ask them if the patient is taking olmesartan, which has occasionally led to a rapid diagnosis and resolution of the problem while under the care of the referring physician, without the patient even coming to our center for formal evaluation. The now established fact that olmesartan is a cause of villous atrophy and sprue-like enteropathy is not a matter of dispute in the medical community. For example, in addition to the FDA safety notification, and many references in the literature, olmesartan is now listed as a *cause* of villous atrophy in the widely-used physician reference Up To Date:

Causes of small intestinal villous atrophy other than celiac disease

Small intestinal bacterial overgrowth
Crohn disease
Cow's milk or soy protein intolerance (children)
Eosinophilic gastroenteritis
Giardiasis
Intestinal lymphoma
Peptic duodenitis
Post-gastroenteritis
Tropical sprue
Zollinger-Ellison syndrome
Common variable immunodeficiency
Autoimmune enteropathy
Other immunodeficiency states (usually apparent clinically, eg, AIDS enteropathy, hypogammaglobulinemic sprue)
Medications (eg, olmesartan)
Whipple disease
Malnutrition
Intestinal tuberculosis
Graft-versus-host disease

Based on my knowledge, education, training, and experience, which includes the diagnosis and treatment of numerous patients with olmesartan enteropathy, my knowledge of the medical literature, and my review and analysis of the documents and information referenced in this report, it is my opinion to a reasonable degree of medical certainty that Olmesartan causes sprue-like enteropathy and related side effects in a subset of patients utilizing the drug, which I refer to as olmesartan enteropathy herein.

I. The Medical Literature

The first mention of the condition that came to be known as olmesartan enteropathy was made in a 2010 case series of collagenous sprue reported by Joseph Murray's group at the Mayo Clinic. Rubio-Tapia, et al. Gluten-Free Diet and Steroid Treatment Are Effective Therapy for

Most Patients with Collagenous Sprue. Clinical Gastroenterology and Hepatology 2010; 8:344-349 This retrospective review consisted of patients with collagenous sprue seen at three Mayo sites (Rochester, Jacksonville and Scottsdale) during the years spanning 1993-2009. Collagenous sprue is a form of enteropathy that is characterized by villous atrophy (characteristic of celiac disease as well) and additionally a thickened band of subepithelial collagen. A total of 30 patients were identified, the great majority of whom (97%) had weight loss, and all of whom had diarrhea. A concomitant diagnosis of celiac disease was noted in 11 (37%) of these patients, though only 6 of these 11 patients had a history of elevated celiac disease serologies. The authors noted that 8 of the 30 patients (27%) had been taking olmesartan; this is especially impressive given that more than half of the time span of this study occurred prior to the approval and availability of olmesartan. The main focus of the paper is on outcomes and response to the gluten-free diet and immunosuppressive therapy, but the authors note the following in the Discussion, when making the point that antifibrotic therapy may not necessarily be effective for this condition: "Indeed, olmesartan, a drug with antifibrotic properties outside the gastrointestinal tract, was used by one third of our patients."

In 2012, Dr. Murray's group published a case series of olmesartan enteropathy consisting of 22 patients, 2 of whom were previously included in their report on collagenous sprue. Rubio-Tapia, et al. Severe spruelike enteropathy associated with olmesartan. Mayo Clin Proc. August 2012;87(8):732-738 All 22 patients had chronic diarrhea, duodenal biopsies showing villous atrophy, alternative causes ruled out, and a clinical improvement after discontinuation of olmesartan. The majority (16/22, 73%) were previously diagnosed with either non-responsive/refractory celiac disease or unclassified sprue. The mean duration of olmesartan use

prior to the development of symptoms was 3.1 years. Weight loss was a prominent symptom, and ≥10 kg of weight loss was reported in 19 of the 22 patients (86%). After olmesartan withdrawal and clinical improvement, a follow-up duodenal biopsy was performed in 18 patients, 17 of whom (94%) had histologic recovery of villous atrophy (while the 18th patient had marked improvement from total villous atrophy to focal partial villous atrophy). All patients improved upon dechallenge, and deliberate rechallenge was not performed due to the severity of the risk; however, the authors note that a rechallenge occurred in the history of 4 patients:

> No deliberate rechallenge test with olmesartan was undertaken because of the life-threatening nature of the syndrome, although 2 patients reported anecdotally that their symptoms had worsened when they restarted olmesartan before the potential association was recognized, and 2 patients experienced improvement when olmesartan was stopped when they were hospitalized (for dehydration and hypotension) and worsened in the weeks following discharge and re- introduction of olmesartan.

Of note, though Dr. Murray's study of patients with olmesartan enteropathy was not discussed in the literature prior to 2012, Daiichi Sankyo was aware of the fact that Dr. Murray was seeing patients with sprue-like symptoms while taking olmesartan medoxomil. Dr. Murray contacted Daiichi Sankyo to inquire of the company as to any information that could be shared regarding "data pertaining to colitis, enteritis, or sprue-like symptoms," in 2009, about "possible side effects of olmesartan, specifically Benicar and the association with unsual and rare enteropathy malapsorption," in 2010, and reporting, "five patients experienced enteropathy like disease while taking olmesartan," in 2011. (Allen Feldman, 370-389, Exhibits 359, 360, 361). As discussed below, by 2009 when Dr. Murray contacted the company (and earlier) Daiichi Sankyo already had received numerous compelling adverse event reports regarding patients with the

clinical syndrome presented with olmesartan enteropathy (i.e. chronic diarrhea, dehydration, severe weight loss, reports of positive dechallenges and rechallenges, hospitalizations).

Following the case series by Dr. Murray's group, additional sporadic case reports were published from institutions in Pennsylvania, Ohio, and Texas. The reference list to this report lists numerous additional case reports. Dreifuss SE1, Tomizawa Y, Farber NJ, Davison JM, Sohnen AE. Spruelike enteropathy associated with olmesartan: an unusual case of severe diarrhea. Case Rep Gastrointest Med. 2013;2013:618071; Stanich PP1, Yearsley M, Meyer MM. Olmesartan-associated sprue-like enteropathy. J Clin Gastroenterol. 2013 Nov-Dec;47(10):894-5; Nielsen JA1, Steephen A, Lewin M. *Angiotensin-II inhibitor (olmesartan)-induced collagenous sprue with resolution following discontinuation of drug.* World J Gastroenterol. 2013 Oct 28;19(40):6928-30. . In addition to these individual case reports, three additional case series were published on this condition in 2013-2014. I co-authored a case series of patients at the Celiac Disease Center at Columbia University on the topic of seronegative villous atrophy, in which we found that 16 of 72 patients with this condition (22%) had olmesartan enteropathy. Olmesartan was the most common cause of drug-induced villous atrophy in our series (16 of 19 patients, 84%). DeGaetani, et al. Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma. Am J Gastroenterol 2013;108:647-653 A case series from a single institution in France described 5 patients with diarrhea attributed to olmesartan, of whom 3 had villous atrophy on duodenal biopsy. Theophile, et al. Five cases of sprue-like enteropathy in patients treated by olmesartan. Dig Liver Dis. 2014 May;46(5):465-9 Another series of 3 patients with villous atrophy attributed to olmesartan was reported by investigators in Rome. Ianiro G1, Bibbò S, Montalto M, Ricci R, Gasbarrini A, Cammarota G. Systematic review: Sprue-like

enteropathy associated with olmesartan. Aliment Pharmacol Ther. 2014 Jul;40(1):16-23. By that time, the accumulating case reports and series were growing at a pace that prompted those writers to include a review of the literature; they found that 54 patients were reported as diagnosed with olmesartan enteropathy to date. See Ianiro, et al.

The first publication to discuss the gastrointestinal effects of olmesartan using a control group was a letter published by two investigators for the ROADMAP study of olmesartan, which was designed to study a primary endpoint of occurrence of microalbuminuria, in reply to Dr. Murray's case series. Menne, Haller. Olmesartan and Intestinal Adverse Effects in the ROADMAP Study. Mayo Clin Proc. December 2012;87(12):1230-1232. This letter reported that, among patients participating in a randomized trial of olmesartan use in diabetics, the development of treatment emergent adverse events was not significantly different among those randomized to olmesartan (3.5%) compared to those randomized to placebo (4.2%, p=0.20). Diarrhea was specifically queried, and this symptom was present in the same proportion of those receiving drug and placebo (2.3%). Although the authors argued that "our observation in a large group of diabetic patients treated with 40 mg of olmesartan daily does not support this conclusion" that olmesartan is directly involved in sprue-like enteropathy, these findings do not rule out causality for an uncommon adverse event that occurs with long-term use of the drug. This analysis consisted of 2,232 patients exposed to olmesartan for a median of 3.2 years. Given that the mean onset to symptoms in Murray's case series was 3.1 years, and given the unknown incidence of olmesartan enteropathy, this subanalysis of a clinical trial is insufficient to assess for causality. Indeed, the purpose of phase 4 evaluation is to test long-term, less common adverse events induced by the drug; a phase 3 study would not be adequately powered to pick up a signal

in the case of a rare event. Moreover, the article published in the New England Journal of Medicine with regard to the study does not discuss gastrointestinal side effects. Haller H, Ito S, Izzo JL Jr, Januszewicz A, Katayama S, Menne J, Mimran A, Rabelink TJ, Ritz E, Ruilope LM, Rump LC, Viberti G; ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med. 2011 Mar 10;364(10):907-17; (Jeffrey Warmke, 192:14-19). The case report forms also do not specify gastrointestinal side effects as an adverse event to be watched, and the investigators were not told about the adverse event reports the company was accumulating for patients with severe gastrointestinal side effects. (Jeffrey Warmke, 109:16-110:3, 110:4-11, 110:12-18, 111:19-112:7, 113:3-20, 145:21-146:11, 157:15-158:5). These factors, combined with the delayed onset of the condition, could have resulted in cases of olmesartan enteropathy being missed. Daiichi Sankyo employee Jeffrey Warmke testified in his deposition that the ROADMAP study was not designed to study gastrointestinal side effects, and was not adequately powered to study gastrointestinal side effects or any of the secondary endpoints of the study, and the study population was different from the general population taking Benicar in the United States. (Jeffrey Warmke, 88:8-15, 111:5-11, 272:19-274:11, 362:12-363:23). Notwithstanding, Dr. Warmke did acknowledge that there were patients who presented with clinical symptoms of olmesartan enteropathy, including dechallenge and rechallenge, and assessment by Daiichi Sankyo as probably related to the drug. This includes one patient who had a documented dechallenge and rechallenge in December, 2006 and January, 2007, and Dr. Warmke acknowledged that Daiichi Sankyo had first hand information that olmesartan likely caused these symptoms. One patient had documented villous atrophy, and another had documented collagenous colitis found by the investigator to be

definitely caused by the drug. (Exhibits 3047, 3048, 3049, 3051; Jeffrey Warmke, 327:21-334:24, 337:2-339:17, 340:14-346:21, 347:15-350:10). The letter to the Mayo Clinic Journal, authored by the lead investigators of the study, does not discuss these specific patients since it was limited to an aggregate analysis of trial participants, and acknowledges that a signal could have been missed due to the limited size and duration of the study. In sum, the ROADMAP study does not disprove association or causality for olmesartan enteropathy, and in fact study patients have been identified who likely developed the condition.

I was the senior investigator of two studies evaluating olmesartan enteropathy that included a control population. In both of these studies, we studied the question of whether the cases of olmesartan enteropathy in the literature represent a "tip of the iceberg" phenomenon. The first study was a case-control study consisting of patients at Columbia University Medical Center who were undergoing upper endoscopy or colonoscopy. Greywoode, et al. Olmesartan, Other Antihypertensives, and Chronic Diarrhea Among Patients Undergoing Endoscopic Procedures: A Case-Control Study. Mayo Clin Proc. September 2014;89(9):1239-1243. We sought to determine whether olmesartan use was more common among patients noting diarrhea as the reason for their procedure as compared to controls who underwent their procedure for another reason. We found that there was no statistically significant association between olmesartan use and diarrhea in this population. However, as we acknowledged in the Discussion section of that paper, "there was also a relatively small prevalence of use of olmesartan (0.7%-1%) among study patients, limiting the power of this analysis. Because the upper bound of our 95% CI was 5.00 in the EGD analysis and 1.74 in the colonoscopy analysis, a meaningful

association between olmesartan and diarrhea may exist that was not detectable because of the relative rarity of use of olmesartan."

Recognizing that the low number of users of olmesartan in our medical center limited our power to detect a signal when using olmesartan exposure as an outcome in a case-control setting, our second study investigating a potential "tip of the iceberg" sampled patients based on exposure to olmesartan. Lagana, et al. Sprue-like histology in patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers. J Clin Pathol 2014;0:1-4. In a cross-sectional study, we compared 20 olmesartan users who underwent duodenal biopsy for evaluation of abdominal pain and compared them to a population of age and sex-matched non-olmesartan controls who also underwent duodenal biopsy for abdominal pain. The outcome of interest was the presence of one or more of the following histologic features: villous atrophy, crypt hyperplasia, mean maximum intraepithelial lymphocyte count, generalized intraepithelial lymphocyte increase, chronic inflammation, eosinophilia, neutrophilia, or increased crypt apoptosis. We found that, although ≥ 1 of these features was present in 50% of the olmesartan group and this was greater than that of controls (20%), this did not meet statistical significance ($p=0.10$). From a statistical standpoint, the study was likely underpowered to detect a signal of subtle histologic abnormalities related to olmesartan. We therefore concluded that: "This study raises the possibility that there may be a spectrum of injury associated with olmesartan use, apart from the severe syndrome that causes life-threatening diarrhea." Of note, we discussed a case report we defined as having "considerable relevance to our study," describing a patient who presented with constipation, but not diarrhea, and varied findings on duodenal biopsy. Talbot GH. Small bowel histopathologic findings suggestive of celiac disease in an asymptomatic

patient receiving olmesartan. Mayo Clin Proc. 2012;87:1231-2 Based on my continued study of olmesartan enteropathy, including reports of patients with variable presentations and clinical symptoms, it is likely that there is a spectrum of injury.

We conducted these two studies so as to better characterize the clinical spectrum of olmesartan enteropathy. The null findings of the case-control study and cross-sectional study suggest that olmesartan is not a common cause of diarrhea among patients undergoing endoscopy, and that olmesartan does not cause far greater histologic abnormalities in individuals who have abdominal pain as compared to those who do not take olmesartan. However, this does not detract from the overall question of causality. These investigations should be seen in the context of studying and defining the boundaries of the condition. The case that the relationship between olmesartan and enteropathy is causal is well established based on the numerous dechallenge studies decribed in the case series and reports above. In general, when adverse effects are events that occur commonly in the general population (such as diabetes or depression), it may be difficult to be certain that the event occurred due to the agent, and abatement of the event after withdrawal of the agent may be suggestive, but not definitive for causality. In contrast, the clinical presentation of olmesartan enteropathy is not commonly seen. For example, one of the findings often seen with this condition, intestinal villous atrophy, has a limited number of causes and does not occur commonly in the general population. Where alternative causes of villous atrophy can be ruled out (e.g. negative celiac serologies, and a lack of a response to a gluten-free diet in the case of celiac disease, and a resolution of villous atrophy after discontinuation of olmesartan despite resumption of a gluten-containing diet), the establishment of causality is straightforward.

In addition to the fact that dechallenge and rechallenge strongly establishes causality, our understanding of this relationship was strengthened by a nationwide cohort study by Basson and colleagues that provided helpful data on the temporality as well as the strength of the relationship. Basson, et al. Severe malabsorption associated with olmesartan: a French nationwide cohort study. Gastroenterology 2014; 146:S-114. In that study, which evaluated more than 4 million adults in France prescribed an ACE inhibitor or an angiotensin receptor blocker (ARB, including olmesartan), the authors found that, compared to users of ACE inhibitors, users of olmesartan had a more than two-fold increased risk of hospitalization for malabsorption overall (adjusted rate ratio [ARR] 2.49; 95%CI 1.73-3.57). Moreover, when stratified by duration of time on the drug, this association was not found among those with <1 year of exposure (ARR 0.76; 95%CI 0.39-1.49) but was markedly increased among those with >2 years of exposure (ARR 10.65; 95%CI 5.05-22.46). This finding, of a large effect size when evaluating long-term use, supports the conclusion that the risk of this outcome is related to the duration of drug use, lending credence to both the strength of association and a biological gradient. The absolute rate of hospitalization for malabsorption occurred in 48 patients over the course of 860,894 person-years. This yields a rate of 5.6 events per 100,000 person-years of observation. Though this is likely an underestimate of the rate of olmesartan enteropathy (given that outpatients with the condition were not counted), the order of magnitude of this rate provides a strong explanation as to why diarrhea was not detected in users of olmesartan in the ROADMAP study; the latter study had an insufficient number of patients followed for an insufficient period of time to detect this adverse event.

It is also notable that the authors found a strong effect size when evaluating olmesartan use for >2 years and a subsequent hospitalization with a discharge diagnosis of celiac disease (ARR 10.21; 95%CI 4.21-24.76). Given the histologic resemblance of olmesartan enteropathy with celiac disease, these patients were likely misdiagnosed with celiac disease, analogous to the numerous patients described as having been diagnosed with celiac disease in adverse event reports to Daiichi Sankyo, and the many misdiagnoses documented in the literature (for example, the patients discussed in the August 2012 Rubio-Tapia article who were initially diagnosed with celiac disease).

The delayed onset of olmesartan enteropathy is described across the literature. This is likely due to the as-yet fully characterized nature of the immune response to this medication. Unlike a classical drug allergy that is typically apparent within 24 hours of initial exposure and is mediated by mast cell activation and/or circulating immunoglobulin E, olmesartan enteropathy typically develops after a prolonged period of drug exposure, congruent with the mean exposure of 3.1 years reported by Murray's group. There are two broad ways to think about how a drug can cause an outcome over long time horizon: accumulated toxicity and a co-factor. An example of accumulated toxicity is the undisputed causal link between cigarette smoking and lung cancer. This adverse effect of cigarette smoking is delayed because the cellular damage and accompanying inflammation that occurs with smoking is cumulative, and multiple resultant genetic mutations need to occur before this results in cancer. Hence the risk of lung cancer rises decades after an individual begins smoking because of the time required to accumulate cellular damage. The second prototype of delayed drug toxicity is that requiring a co-factor. For example, Reye's Syndrome, a rapidly progressive illness characterized by encephalopathy and

liver failure, was linked to aspirin use by children, but this condition only develops in the context of an acute viral illness, a co-factor that is necessary for the development of this drug-mediated illness. The present evidence points to this latter mechanism of a co-factor that triggers olmesartan enteropathy. Just as individuals at any age can develop celiac disease, in which gluten induces villous atrophy after years of gluten exposure without ill effect, olmesartan (like gluten in celiac disease) likely requires an as-yet unidentified co-factor upon which exposure to this drug induces villous atrophy. (It should be noted that the co-factor that triggers celiac disease in individuals after years of gluten exposure has not been identified, but this does not at all undercut the indisputable causal link between gluten and villous atrophy among patients with celiac disease.)

The mechanistic study by Dr. Murray's group points to a biologically plausible mechanism by which olmesartan induces enteropathy after a variable period of exposure. Marietta EV, Nadeau AM, Cartee AK, Singh I, Rishi A, Choung RS, Wu TT, Rubio-Tapia A and Murray JA. Immunopathogenesis of olmesartan-associated enteropathy. Aliment Pharmacol Ther. 2015 Dec;42(11):1303-14. This study consisted of immunohistochemical analysis of patients with known olmesartan enteropathy (including patients both on and off olmesartan) as well as immunofluorescent analysis of generic human intestinal epithelial cells (Caco2 cells) after in vitro incubation with olmesartan for 4 hours. The authors found that incubation of these cells with olmesartan resulted in the expression of IL-15, a cytokine that has been broadly implicated in refractory celiac disease. Malamut G, et al. *IL-15 triggers an antiapoptotic pathway in human intraepithelial lymphocytes that is a potential new target in celiac disease-associated inflammation and lymphomagenesis.* J Clin Invest. 2010 Jun;120(6):2131-43. When

incubating these cells with losartan and telmisartan, this finding was not observed. This *in vitro* demonstration of a pro-inflammatory cytokine release (particularly one that is closely associated with refractory celiac disease, a histologic mimicker of this condition), one that is specific to olmesartan among members to this drug class, adds biologic plausibility to the case for causality. Stated another way, this study likely establishes the biological mechanism whereby olmesartan causes this clinical syndrome. As recognized by Daiichi Sankyo, olmesartan clearly causes biological changes to the small intestine, leading to some or all of the findings and symptoms of olmesartan enteropathy, including inflammation, villous atrophy, malabsorption, chronic diarrhea and/or vomiting, dehydration, abdominal pain, nausea, and severe weight loss, and in some patients systemic effects due to the resulting lack of absorbed nutrients.

A. Variation In Clinical Presentation of Olmesartan Enteropathy

It is important to discuss the variable presentation of olmesartan enteropathy, in terms of the clinical presentation and severity of symptoms. There is literature supporting a spectrum of severity, with varied clinical pictures, likely due to the stage of development of the syndrome. For example, the French nationwide cohort study by Basson, et al [Basson M, Mezzarobba M, Weill A, Ricordeau P, Allemand H, Alla F and Carbonnel F. Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. Gut. 2016 Oct;65(10):1664-9] was restricted by definition to those who whose clinical condition was sufficiently severe so as to warrant hospitalization, while in the case series by Rubio-Tapia, et al [Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT and Murray, JA. Severe Spruelike Enteropathy Associated With Olmesartan. Mayo Clin Proc. 2012 Aug;87(8):732-8. Epub 2012 Jun 22.] 36% of patients did not require hospitalization. It is also

possible that patients with mild or minimal symptoms but with laboratory abnormalities could have an attenuated form of this condition. This was suggested by Talbot, et al who described a patient who was taking olmesartan and had anemia and reflux; though he did not have diarrhea, he was found to have mild villous blunting and increased intraepithelial lymphocytosis, akin to a mild form of celiac disease.Talbot GH. Small bowel histopathologic findings suggestive of celiac disease in an asymptomatic patient receiving olmesartan. Mayo Clin Proc. 2012 Dec;87(12):1231-2. Though there is less certainty regarding the scope of a mild form of olmesartan enteropathy, given the wide spectrum of clinical severity documented in celiac disease, together with the fact that the majority of patients with celiac disease are undiagnosed, it is reasonable to conclude that there is a clinical and histologic spectrum of severity for olmesartan enteropathy, wherein the more mild cases go undetected and untreated. Rubio-Tapia A1, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. Am J Gastroenterol. 2012 Oct;107(10):1538-44; quiz 1537, 1545. doi: 10.1038/ajg.2012.219. Epub 2012 Jul 31.

This opinion is further supported by additional reports in the literature. One article addressing two cases reports of olmesartan enteropathy discusses the potential for a "patchy" presentation in the duodenum, and, "that olmesartan-associated enteropathy is a new entity with a wide spectrum of histological small bowel abnormalities." Schiepatti, et al. **Olmesartan-associated enteropathy: new insights on the natural history? Report of two cases.** Scandinavian Journal of Gastroenterology. 2015; Early Online: 1-5. Another article, cited in Schiepatti, et al., states: "We report four patients with olmesartan-associated enteropathy and normal villi. The clinical picture was that of severe diarrhoea, similar with that of patients with

villous atrophy, and these four patients also improved after olmesartan withdrawal. These cases add to the description of olmesartan-associated enteropathy. It may include patients with a wide range of histological duodenal abnormalities, from isolated intra-epithelial lymphocytosis and lamina propria lymphocytic infiltration to total villous atrophy. In addition, there is evidence of involvement of almost the entire gut in this condition." In terms of causation, the authors state: "This study supports the causality of the association between olmesartan and enteropathy. Firstly, our cases and those reported by Rubio Tapia et al. were remarkably similar. Secondly, nondeliberate interruptions followed by reintroductions led to clinical remissions followed by clinical relapses repectively. Thirdly, as in the study by Rubio Tapia et al., duodenal mucosa returned to normal after olmesartan withdrawal." Marthey, et al. **Olmesartan-associated enteropathy: results of a national survey.** Aliment Pharmacol Ther 2014; 40: 1103-1109.

Another case report discusses a patient with olmesartan enteropathy who suffered a colon perforation, in a patient reporting, "recurrent mild abdominal pain, bloating, nausea, occasional vomiting, and severe nonbloody diarrhea with 20 evacuations a day for one year. She had a 45 pound weight loss with six months…Celiac disease was excluded by negative conventional serology tests…and the absence of a clinical response to a gluten-free diet…Olmesartan associated enteropathy was suspected and the drug was discontinued and replaced by lisinopril. One month later, she had complete resolution of the abdominal discomfort and diarrhea. After 5 months the patient continued to be asymptomatic with no gastrointestinal manifestations." Abdelghany, et al. **Olmesartan Associated Sprue-Like Enteropathy and Colon Perforation.** Case Reports in Gastrointestinal Medicine. Volume 2014, Article ID 494098, 2014.

B. Resulting Systemic Harm From Olmesartan Enteropathy

Malabsorption has clinical consequences that go beyond the acute presentation of dehydration, diarrhea, vomiting, and weight loss. Celiac disease is known to cause a wide range of such systemic consequences, and the similar manifestation of olmesartan enteropathy exposes the patient to a similar spectrum of harms.. The list of systemic harms resulting from olmesartan enteropathy may include, in no particular order of importance or frequency, steatorrhea, fatigue or weakness, neuropathy, hair loss, muscle wasting, renal compromise and damage, anemia, and others. These symptoms can have a significant detrimental impact on a patient's quality of life. Based on our knowledge of the impact of celiac disease on morbidity, we can infer that there is analogous burden among those with olmesartan enteropathy. For instance, anemia is a common consequence of malabsorption, as has been observed both in celiac disease [Abu Daya H1, Lebwohl B, Lewis SK, Green PH. Celiac disease patients presenting with anemia have more severe disease than those presenting with diarrhea. Clin Gastroenterol Hepatol. 2013 Nov;11(11):1472-7.] and olmesartan enteropathy (present in 45% of patients in one systematic review).[Ianiro G1, Bibbò S, Montalto M, Ricci R, Gasbarrini A, Cammarota G. Systematic review: Sprue-like enteropathy associated with olmesartan. Aliment Pharmacol Ther. 2014 Jul;40(1):16-23..] This can result in significant fatigue and can take months to reverse. Moreover, many patients with olmesartan enteropathy were treated with corticosteroids in addition to a gluten-free diet; this was the case in 20 of the 22 patients (91%) in Rubio-Tapia's initial case series.[Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT

and Murray, JA. Severe Spruelike Enteropathy Associated With Olmesartan. Mayo Clin Proc. 2012 Aug;87(8):732-8] Corticosteroid treatment can have numerous adverse consequences, both short-term (including hyperglycemia, neuropsychiatric symptoms, and swelling in the extremities and face) and long-term (cataracts and worsened bone density, increasing the risk of fracture). Since many patients with olmesartan enteropathy have been and likely continue to be treated with a gluten-free diet under the erroneous impression of a celiac disease diagnosis, the burden of this diet should be considered. This diet is expensive, socially isolating, and can impair quality of life; patients with celiac disease who are maintaining this diet have rated its burden as considerable.

Shah S, Akbari M, Vanga R, Kelly CP, Hansen J, Theethira T, Tariq S, Dennis M, Leffler DA. Patient perception of treatment burden is high in celiac disease compared with other common conditions. Am J Gastroenterol. 2014 Sep;109(9):1304-11.

II. Methodology

The clinical process to identify olmesartan enteropathy as the likely cause of a patient's symptoms is one of differential diagnosis. In our publication on seronegative villous atrophy, DeGaetani, et al., we discuss the following diagnostic algorithm:

> We propose that all patients with seronegative VA should initially be tested for HLA DQ2 and DQ8. If the test is negative, we would usually exclude CD. Immunoglobulin deficiency should also be excluded, both selective IgA deficiency and CVID. A thorough history should be obtained, which should include medication and travel history.

In clinical practice, this translates into the assessment for use of olmesartan (and other medications) during the initial history taking. Among patients with villous atrophy who report

taking olmesartan, at our institution we have deemed the causality to be so strong in this group of patients that we advise discontinuing olmesartan and switching to an alternative anti-hypertensive agent in consultation with the prescriber of that medication (e.g. the patient's internist or cardiologist who is treating the patient's hypertension). In my experience patients with seronegative villous atrophy who were taking olmesartan at the time of assessment had resolution or marked improvement of symptoms and villous atrophy upon discontinuation of the drug. An illustrative Case Report regarding a patient hospitalized three times for severe dehydration and acute renal failure, later found to have olmesartan enteropathy, describes this approach: "Olmesartan-induced enteropathy should be in the differential diagnosis for patients who present with severe unexplained chronic diarrhea and weight loss. Moreover, in patients with a working diagnosis of CD but negative CD-specific serology or lack of response to a gluten-free diet, a review of current medications is desirable before resorting to other expensive investigations." Rishi, A., Garland, K. Unusual Severe Side Effect of a Commonly Used Drug. Journal of Clinical Hypertension, 2015.

There is a spectrum of potential causes for the combination of symptoms that is seen with olmesartan enteropathy. In the evaluation of causation for a particular patient, the generally applicable components of the differential diagnosis will usually include celiac disease (discussed above), as well as irritable bowel syndrome (ulcerative colitis, Crohn's disease), autoimmune enteropathy, and medication induced enteropathy. The appropriate differential for a particular patient is established through application of this general process, informed by a thorough history and physical exam, with particular attention to co-morbidities, time of onset, nature of the symptoms, medications, and other medically significant facts. Other potential causes may merit

consideration based on this process. One must then evaluate the clinical course, particularly dechallenges and rechallenges, in ruling out/in aspects of the differential diagnosis.

Of particular importance are documented dechallenges, and even more so, rechallenges. This information is important not just from a clinical perspective, but also from an epidemiological perspective. When determining whether a drug is associated with an adverse outcome, the strength of association depends on certain aspects of each case, including temporality (i.e. that the adverse event did not pre-date the exposure to the drug) and abatement of the adverse effect after withdrawal of the drug (i.e. dechallenge). The recurrence of the adverse effect after the resumption of the medication provides particularly strong evidence that an adverse drug effect is occurring. Though case reports are generally low on the hierarchy of evidence when assessing for causality, evidence from a rechallenge is particularly strong. To cite a textbook of pharmacoepidemiology, Strom B, Kimmel S, Hennessey S. Textbook of Pharmacoepidemiology 2nd edition p23.:

> Case reports can be particularly useful to document causation when the treatment causes a change in disease course which is reversible, such that the patient returns to his or her untreated state when the exposure is withdrawn, can be treated again, and when the change returns upon repeat treatment.

Scoring systems, such as the Naranjo algorithm, a widely used method for grading suspicion of causality, place special emphasis on rechallenge.[García-Cortés M1, Lucena MI, Pachkoria K, Borraz Y, Hidalgo R, Andrade RJ; Spanish Group for the Study of Drug-induced Liver Disease (grupo de Estudio para las Hepatopatías Asociadas a Medicamentos, Geham). Evaluation of Naranjo adverse drug reactions probability scale in causality assessment of drug-induced liver injury. Aliment Pharmacol Ther. 2008 May;27(9):780-9.] In the Naranjo algorithm, the greatest

number of points (+2) are assigned to the following two parameters: 1) occurrence of the event after exposure to the drug; and 2) in individual cases a positive rechallenge. As noted above, the original case series by Rubio-Tapia noted that a deliberate rechallenge was not performed but that 4 of the 22 patients had experienced a recurrence of symptoms upon reintroduction of the medication, a *de facto* rechallenge.[Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT and Murray, JA. Severe Spruelike Enteropathy Associated With Olmesartan. Mayo Clin Proc. 2012 Aug;87(8):732-8] Rechallenge evidence was also noted in the Medwatch report cited above (Medwatch report number SU-2007-005968).

The evidence to be presented below will consider the Bradford Hill criteria for causality. Strom, et al. These criteria consist of biological plausibility (see above under Medical Literature),[Marietta EV, Nadeau AM, Cartee AK, Singh I, Rishi A, Choung RS, Wu TT, Rubio-Tapia A and Murray JA. Immunopathogenesis of olmesartan-associated enteropathy. Aliment Pharmacol Ther. 2015 Dec;42(11):1303-14.] the strength of the association (see rate ratios reported below by Basson, et al [Basson M, Mezzarobba M, Weill A, Ricordeau P, Allemand H, Alla F and Carbonnel F. Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. Gut. 2016 Oct;65(10):1664-9.], the consistency of symptomatology (see adverse event reports and case series below), specificity (the paucity of sprue-like enteropathy reported in other antihypertensives and the quantititative difference when comparing olmesartan use to angiotensin converting enzyme inhibitors),[Basson M, Mezzarobba M, Weill A, Ricordeau P, Allemand H, Alla F and Carbonnel F. Severe intestinal malabsorption

associated with olmesartan: a French nationwide observational cohort study. Gut. 2016 Oct;65(10):1664-9.] and temporality (see adverse event reports and case series below).

The term "associated" rather than "induced" was initially used by Dr. Murray, likely due to his exercising caution when describing a new entity, mindful of the ever-present scientific practice to avoid confusing correlation with causation. The magnitude of the clinical improvement upon dechallenge in his and our case series and the absence of suspicious confounding variables in the cases described left little doubt that olmesartan was causing this syndrome, but the condition continued to be described as "associated with olmesartan" as reports accrued in the literature, in following the convention of naming this newly-defined condition. In fact, there are statements recognizing causality in more recent publications on which Dr. Murray is a co-author. One states: "All of these reports clearly demonstrate that administration of olmesartan to some individuals can lead to severe enteropathy." Marietta, et al. Drug-Induced Enteropathy. Digestive Diseases 2015;33:215-220. In another, "Olmesartan appears to cause a spruelike enteropathy, but it has not been shown to trigger celiac disease per se," and then at the end recognizes that olmesartan, "induces VA." Marild, et al. Blockers of Angiotensin Other Than Olmesartan in Patients With Villous Atrophy: A Nationwide Case-Control Study. Mayo Clin Proc. 2015;90(6):730-737. In an invited editorial authored with J.F. Ludvigsson, one of my co-authors in the Marild, et al. article, we stated in part: "when one considers a more specialised population, such as those referred to a coeliac disease centre for seronegative villous atrophy or those with collagenous sprue, olmesartan appears to be a prominent, even common, cause of these uncommon conditions." Lebwohl, B., Ludvigsson, J.F. Editorial: sprue-like enteropathy due to

olmesartan and other angiotensin receptor blockers – the plot thickens. Aliment Pharmacol Ther 2014; 40:1241-1249. In addition, the FDA states: "The U.S. Food and Drug Administration (FDA) is warning that the blood pressure drug olmesartan medoxomil (marketed as Benicar, Benicar HCT, Azor, Tribenzor, and generics) can cause intestinal problems known as sprue-like enteropathy." FDA Drug Safety Communication: FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil. July 3, 2013 (Note: This report does not address any opinions regarding the adequacy of the warning added to the label). I was also co-author of an article recognizing causality prior to the FDA Safety Communication was issued, indicating, "before identifying olmesartan as a cause of VA, we too had considered 30% of our seronegative patients to have [unclassified sprue]." DeGaetani, et al. Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma. Am J Gastroenterol 2013;108:647-653. While caution when attributing causality is a prudent scientific habit at the outset as data is generated, in the case of olmesartan enteropathy, sufficient evidence has accumulated so as to conclude that this drug causes enteropathy in a subset of patients.

III. Adverse Event Reports

I have reviewed a number of adverse event reports produced from the files of Daiichi Sankyo, documenting patients exhibiting symptoms of olmesartan enteropathy. The adverse event reports present numerous cases supporting the finding of causation, dating back to 2003. Perhaps most significant is the repeated presentation of this clinical syndrome, inclusive of dechallenges successfully improving or alleviating the symptoms, and rechallenges resulting in

the return of clinical symptoms. I have independently evaluated a number of these adverse event reports and determined that a significant number present cases of olmesartan causality. It is important to recognize that it is an "accepted fact" that adverse events are underreported, as acknowledged by Dr. Allen Feldman of Daiichi Sankyo. (Allen Feldman, 144-145).

Before addressing several MedWatch forms as examples of the numerous reports I have reviewed, I address the methodology of my approach. As with the general approach to assessing the cause of symptoms as discussed above, I formed a differential diagnosis, applied my medical judgment, and used the information available to rule out and rule in potential causes reasonably included in the differential diagnosis. This is the approach utilized by the physicians performing the causality assessments, where performed. In the context of clinical study adverse events, Tina Ho testified: "the medical review specifically is for someone with the medical credential to look at the information and confirm especially the causality." This is referred to as a "clinical evaluation of the case." The company protocol required the medical reviewer, "to ensure accuracy and completeness from the clinical perspective." (Tina Ho, 569-575). With regard to the assessment and reporting of adverse events from non-study sources, Tina Ho testified regarding the company's protocols, RM-SOI-003, including the criteria and methodology for medical doctors to perform the causality assessments on serious adverse events. Tina Ho confirmed: "you want doctors exercising medical judgment, evaluating the relevant information that's available to your company to form this judgment, this opinion.." From 2007 to 2009 the definitions utilized were adopted from the WHO-UMC Causality Categories – including definitely related, probably related, possibly related, unlikely related, and unknown (where there is not adequate information to form a valid medical judgment). Tina Ho agreed that in each case,

based on the available information, "you have a medical doctor looking at all of the available information and the person to be able to say, assess that it's probably related, when they're looking at the known characteristics of the subject's clinical state, that's differential diagnosis; that's looking at what disease does the person have, what's their comorbidities, what other drugs were they taking, I mean, looking at their whole picture.." Finally, and most important, "**In the individual case that's being evaluated, if either probably related or definitely related is checked, that means the medical reviewer felt that in that patient's case, the side effect being looked at was likely caused by the drug for that patient.**" (Tina Ho, 606:24-617:14). In April, 2009 the SOI was modified to limit the available labels to related or unrelated, however Tina Ho confirmed the same process would be followed as with the former criteria, and a finding of related would equate to the top half of the list and a finding of unrelated would equate to the bottom half of the list. (Tina Ho, 619-620). The criteria for the protocols governing evaluation of adverse events from clinical studies were essentially the same, and were also changed in April, 2009 to simplify to related and unrelated. In discussing a powerpoint illustrating that change in terminology, Tina Ho confirmed, "there's actually definitions of the related and not related, which, again, just lumps in the different clinical criteria that the medical reviewer would be applying and doing a differential and exercising medical judgment." (Tina Ho, 632-633). Finally, Tina Ho confirmed that the related/unrelated terminology is not something created by Daiichi Sankyo, it is "a validated industry standard methodology." (Tina Ho, 627-628).

Tina Ho was presented with a MedWatch report for an adverse event reported to Daiichi Sankyo by a physician on October 19, 2006. The reported clinical information included diarrhea and vomiting, weight loss, hospitalizations, and a positive dechallenge, then a positive

rechallenge. The causality was assessed as "definite." Tina Ho confirmed, "the medical doctor who evaluated this agreed that, you know, when we have a rechallenge here, in light of all the other information, there's a definite relationship." (Tina Ho, 621:7-623:12). My independent evaluation of this report is consistent with that of the reporter and the medical reviewer at Daiichi Sankyo.

Medwatch report number SU-2007-005968, bates number OLM-DSI-0004774183, deposition exhibit 347, reported to Daiichi Sankyo on March 22, 2007, discusses a patient with reported massive diarrhea, severe dehydration, and a 20 pound weight loss. There is positive dechallenge and positive rechallenge, as the symptoms abated when the medication was stopped, and the symptoms recurred when the medication was restarted. This clinical picture fits well with the clinical picture of patients discussed in Rubio-Tapia, and the numerous pertinent studies and case reports in the literature. Although there is no biopsy referenced, and no celiac disease testing referenced, a clinical diagnosis can be formed to a reasonable degree of medical certainty that the most likely cause of the clinical presentation discussed is the olmesartan. This is because the clinical symptoms are consistent, and the documented dechallenge and rechallenge is essentially decisive clinical information since it is medically improbable that there could be a different cause such as celiac disease, IBD, or autoimmune enteropathy, with the symptoms abating and/or recurring in correlation to whether or not the patient was using olmesartan. It should also be noted that the rate of duodenal biopsy is low in comparison to the number of patients with clinical indications for biopsy during upper endoscopy, so there may be a large number of patients with olmesartan enteropathy but no biopsy. Lebwohl, et al. **Sex and racial disparities in duodenal biopsy to evaluate for celiac disease.** Gastrointest Endosc

2012;76:779-85. If this patient were presented to our practice, in person or for phone consultation, as often happens, the leading diagnosis would be olmesartan enteropathy. Allen Feldman, a medical doctor and the Vice President of Pharmacovigilance at Daiichi Sankyo testified in his deposition that the only plausible cause of this patient's illness was olmesartan (Feldman, 273-274, 283-285), which is further corroboration of the opinion that this is a case of olmesartan enteropathy, and this report stands as additional corroboration that olmesartan causes these symptoms. Yasushi Hasebe, the global head of CSPV, based in Japan, was questioned about another adverse event report, and agreed, "that the olmesartan was one of the factors causing the severe diarrhea, dehydration, and hospitalizations described..." (Yasushi Hasebe, 173). These acknowledgements of causality demonstrate CSPV's understanding and acceptance of causality.

Another illustrative example of an adverse event of interest was described by Jeffrey Warmke, the Daiichi Sankyo employee who testified regarding the ROADMAP study. In reviewing an adverse event for a 56 year old female ROADMAP study patient who was in the olmesartan arm of the study, he acknowledged symptoms including diarrhea and vomiting, resulting in hospitalization. The symptoms ceased when the drug was withdrawn, and resumed when the drug was resumed on December 3, 2006 on release from the hospital. The working diagnoses were gastroenteritis and hypokalemia. (Note that per Mr. Warmke, the study investigators were not informed about the adverse event reports indicating severe gastrointestinal symptoms Daiichi Sankyo was seeing, 111-113,145-146, 157-158). The medication was fully discontinued on December 30, 2006, and the patient was fully recovered by January 31, 2007. Both the investigator and the company assessed the causality as probably related for the

gastroenteritis and hospitalization, with which I concur based on my independent evaluation of the report. Mr. Warmke confirmed that Daiichi Sankyo had first hand knowledge that olmesartan likely caused these symptoms, as this was a study sponsored by Daiichi Sankyo. (Jeffrey Warmke, 327-334).

A recurring issue in a number of the adverse event reports is inclusion of a celiac disease diagnosis in the narrative and/or as a preferred term. This is not surprising, and certainly is not a coincidence, since the symptoms of olmesartan enteropathy are quite similar to celiac disease, and the physicians treating these patients were not likely aware of the risk of olmesartan enteropathy. The recurrent mention of celiac disease in the medical history of adverse event reports points to misdiagnosis of celiac disease during the diagnostic workup of patients who developed olmesartan enteropathy. The literature recognizes the likelihood of physicians misdiagnosing olmesartan enteropathy as celiac disease where the diagnosing physician is not aware of olmesartan enteropathy to be included in the differential diagnosis. Burbure, et al. Olmesartan-associated sprue-like enteropathy: a systematic review with emphasis on histopathology. Human Pathology (2016) 50, 127-134.; Marthey L, Cadiot G, Seksik P and Pouderoux P. *Olmesartan-associated enteropathy: results of a national survey*. Aliment Pharmacol Ther. 2014 Nov;40(9):1103-9. . Indeed, in the initial case series describing olmesartan enteropathy, all patients had been treated initially with a gluten-free diet under the initial impression that the diagnosis was celiac disease. Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT and Murray, JA. Severe Spruelike Enteropathy Associated With Olmesartan. Mayo Clin Proc. 2012 Aug;87(8):732-8. In each of these cases, the onset of the symptoms occurred only after the patient began to use olmesartan, providing a temporal

likelihood, especially since it would be unlikely and coincidental for a patient to suddenly develop celiac disease as an adult while using of olmesartan, and it would be virtually impossible for a patient to spontaneously regain tolerance to gluten if the diagnosis were celiac disease, as in each of these cases the patients had successful dechallenges. Application of a differential diagnosis to the information found in these reports establishes that the likely cause of these patients' symptoms was olmesartan in all, or nearly all of these cases.

The likelihood of misdiagnosis of olmesartan enteropathy as celiac disease can be illustrated with specific adverse event reports. For example, a MedWatch for an adverse event reported to Daiichi Sankyo on July 14, 2005, documents a 36 year old male who developed severe vomiting, diarrhea, and weight loss about one year after starting Benicar HCT. The patient was reported to have two positive dechallenges and a positive rechallenge. The patient was "recently" diagnosed with celiac disease. (SU-2005-003790; OLM-DSI-0001099841). Based upon the information documented in the MedWatch this is likely a case of olmesartan enteropathy, based upon the delayed onset of symptoms, the nature of the symptoms, and the positive dechallenges and rechallenge. The recent diagnosis of celiac disease is confounded by the clinical history, particularly the dechallenges and rechallenge, which would not occur in the setting of celiac disease. It is also noteworthy that this report was not included in the analysis of celiac cases prepared by Herve Caspard of CSPV, and Mr. Caspard did acknowledge in his deposition that it should have been included. (Caspard, 290-298). Another example is a MedWatch documenting an adverse event reported to Daiichi Sankyo on September 15, 2005, with regard to a 58 year old female patient who took Benicar for two years then experienced nausea, vomiting, dehydration, and was hospitalized two times. The report and source files

document positive dechallenge and rechallenge. The patient was diagnosed with celiac disease on the day the patient finally stopped taking the drug, after all the symptoms had manifested and after a positive dechallenge and positive rechallenge. (Note: the report indicates that after ceasing the drug on August 31, 2005 the dehydration had resolved, but the status of the low BP, nausea, and vomiting was unknown as of the date of the report, September 15, 2015) Based on the information in the report, this too is likely olmesartan enteropathy, based upon the delayed onset, nature of the symptoms, and the dechallenges and rechallenge. Tina Ho admitted this report should have been included in the celiac report, but was not. (Tina Ho, 427). Herve Caspard authored emails at the time the report was prepared notifying Allen Feldman that this report should have been included in the celiac report, yet it still was not included. (Allen Feldman, 329-330, Exhibit 355). In terms of causality, these reports further support and corroborate the causality for olmesartan enteropathy.

IV. Internal Documents Addressing Olmesartan Enteropathy

Daiichi Sankyo's internal documents provide foundational information that is helpful in understanding the nature of Olmesartan enteropathy, and the causality. Physicians rely upon information provided by a manufacturer regarding a medication's risks, thus documents and testimony demonstrating what was known but not disclosed is significant since that information, if provided to physicians and patients would be considered and relied on in making treatment decisions. In this context, there are numerous internal documents, and deposition testimony, in which Daiichi Sankyo's employees recognize the causality for olmesartan enteropathy.

Dr. Allen Feldman was the Vice President, Clinical Safety and Pharmacovigilance ("CSPV"), for Daiichi Sankyo in the United States, from June, 2004 to February, 2016. (Allen Feldman, 30-35). One of the key functions of CSPV is to evaluate reports of adverse events to determine if there is a "signal," meaning information that is unexpected and warrants further review. (Allen Feldman, 68:5-18). A signal can be a syndrome or a combination or constellation of symptoms being reported. (Allen Feldman, 126-127). In looking for signals, a foundational source of information is spontaneous case reports, looking in particular at the temporal sequence, and positive dechallenges and rechallenges. (Allen Feldman, 130-131, 135-137). In this context, Dr. Feldman testified that olmesartan was not intended to have any impacts on the gastrointestinal system, and olmesartan was not expected to cause dehydration, weight loss, villous atrophy, lymphocytic colitis, or microscopic colitis, sprue-like enteropathy or a constellation of symptoms that would look like celiac disease. (Allen Feldman, 69:21-70:10, 76-77, 495-497). Dr. Feldman was asked about a series of adverse event reports demonstrating the clinical syndrome consistent with olmesartan enteropathy, (Allen Feldman, 158-169, 169-172, 185-187, 200-204, 204-206, 228-229, 237-238, 250-254, 260-272, 273-274), and acknowledged that the signal was not seen as these reports came into the company in 2005-2007, and that these cases present a strong signal for this collection of symptoms associated with olmesartan. (Allen Feldman, 257-260, 276-282).

Dr. Feldman testified that the clinical syndrome presented in a March 22, 2007 adverse event report was most likely caused by olmesartan, based on the information set forth, and the only plausible cause was olmesartan. (Allen Feldman, 283-285). Of particular significance, Dr. Feldman also agreed that there was an association, and the only likely cause he could advance

for the clinical syndrome presented by the 22 patients in the Rubio-Tapia Mayo Clinic study was olmesartan, based on the clinical picture including that the symptoms started after the patients started taking the drug, the patients had negative celiac serologies and did not respond to a gluten-free diet, and the patients had positive dechallenges. (Allen Feldman, 181-185). These admissions of causation, with which I agree based upon my independent analysis, by the head of the department responsible to analyze this issue, is strong corroboration and fully consistent with the literature in this area. It is important to note that where Dr. Feldman and other Daiichi Sankyo employees have denied that there is proof that olmesartan causes this syndrome, they have done so with no support, and certainly no support in the peer-reviewed medical literature.

Dr. Feldman was also questioned about a series of reports prepared by Daiichi Sankyo, for internal use, and in some instances to be shared with the FDA, analyzing the adverse event reports the company was receiving. Most important, none of these reports disproves the causality for olmesartan enteropathy. The reports include a November 8, 2010 report prepared to assess 279 adverse event reports of diarrhea received by Daiichi Sankyo between 2002 and 2010. This significant number of reports of diarrhea with olmesartan is consistent with the side effect of severe diarrhea known to occur with the drug, though the report did not assess for clinical details, severity, or causality. Another is the November 12, 2009 report by Dr. Ronke Dosunmu, titled "Olmesartan, olmesartan HCT, and celiac disease." Dr. Donsunmu was concerned about the information she analyzed and recommended further investigation to determine whether a risk needed to be added to the warning. (Allen Feldman, 301-314). This and the January 13, 2010 report authored by Herve Caspard, on the potential association between olmesartan and celiac disease for the FDA are significant for the fact that the company was receiving a large number of

reports indicating a celiac disease diagnosis since misdiagnosis of olmesartan enteropathy as celiac disease is known to occur, especially where the clinician is not aware of the connection between olmesartan and the clinical presentation. The confirmed fact that olmesartan does not contain gluten only strengthens the significance of these reports. (Allen Feldman, 311). Herve Caspard, the CSPV employee who authored the celiac report for the FDA, which correctly concluded that olmesartan does not cause celiac disease, but failed to include all celiac disease cases known to Daiichi Sankyo (See discussion of celiac disease adverse event reports above), and failed to address the causality for **celiac-like** symptoms, also performed a proportional reporting ratio ("PRR") analysis of the FDA database for celiac disease reports. Dr. Caspard calculated a 23.36 PRR, which was admitted to be a "very high" number, indicating a signal for celiac disease, per Allen Feldman, and per Herve Caspard indicating a statistically significant association. (Allen Feldman, 345, 351; Herve Caspard, 90-94, 104-108, 124, 127). Another of the reports was the September 28, 2012 report on Sprue-like enteropathy, authored by Crawford Parker of CSPV. The report recognizes the significance of the reports of positive rechallenges, and does not in any way disprove causality. In this context, it is interesting to note that Dr. Joseph Murray of the Mayo Clinic, and the senior author of the Rubio-Tapia and Martietta articles, contacted Daiichi Sankyo in 2009, 2010, and 2011 to discuss and obtain information as he was treating a growing number of patients with refractory celiac diagnoses who were using olmesartan. (Allen Feldman, 369-389). Ultimately, Tina Ho confirmed that the people coding the adverse event reports were told that a report of villous atrophy should be deemed sprue-like enteropathy and the syndrome is referred to in the internal memorandum as olmesartan induced enteropathy. (Tina Ho, 460-467; OLM-DSC-0000221307-08). In this context, I have also

reviewed the June 2013 FDA Mini-Sentinel analysis, which showed a higher rate of celiac disease associated with olmesartan use, than for the other ARB's, with a minimum of 2 years exposure.

Hideki Tagawa is a manager in CSPV. (Hideki Tagawa, 11:5-10). Mr. Tagawa discussed an internal powerpoint describing the characteristic symptoms and findings, as well as diagnosis and treatment, for sprue-like enteropathy. The symptoms and findings listed include: severe diarrhea with weight loss, biopsies sometimes reveal intestinal villous atrophy, and inflammation of the lining of the small intestine, and histopathological improvement and improved clinical symptoms when the drug is discontinued. The symptoms listed also include fatty stools, chronic diarrhea, swelling, abdominal bloating, inflammation of skin, tendency to bleed easily, and anemia. The physical exam findings listed include palpebral conjunctiva, oral mucosa, pale skin, pleural fluid, abdominal dropsy, and emaciation (defined as loss of greater than 20% of standard body weight). Finally, the powerpoint indicates that the drug should be discontinued if it is causing the symptoms, an acknowledgment of cauastion. (Hideki Tagawa, 73-77). Within the same powerpoint is discussion of a fatal sprue-like enteropathy case, where a 70 year old patient had severe diarrhea, dehydration, and a 30 kg weight loss. The conclusion by Daiichi Sankyo is that "causality cannot be denied based on available information," and confirms the drug was the cause of death. (Hideki Tagawa, 57-60). Mr. Tagawa also confirmed that another Japanese language document indicated that the Japanese label was modified to include information about sprue-like enteropathy, because "for the symptoms of severe diarrhea, a causal relationship with drugs containing olmesartan could not be denied." (Hideki Tagawa, 69-70).

Another document containing a very clear statement of causality is the March 7, 2014 "Risk Management Plan for Olmesartan medoxomil/Hydrochlorothiazide." (Discussed in Tina Ho deposition, November 15, 2016, pages 548-564, Exhibit 731). Tina Ho confirmed that this document was required to be submitted to European regulatory authorities and the information would have to be accurate. (Tina Ho, 550:13-19). First, the Summary of Safety Concerns at table 6, page 63, lists one of the identified risks of olmesartan as "sprue-like enteropathy." The other identified risks listed in the table include hyperkalemia, and hypotension. This is consistent with the overwhelming scientific consensus. The "risk minimization measures" for olmesartan states: "increase awareness of the risk of sprue-like enteropathy and provide guidance on how to manage that risk," which Tina Ho confirmed Daiichi Sankyo also tried to do in the United States, by updating the label. (Tina Ho, 556:25-558:10). The document quotes language to be used in the European label for olmesartan, indicating that the "undesirable effects" section will add: "sprue-like enteropathy will be added as a very rare adverse reaction for the monosubstance olmesartan," which means: "some people, however you would define very rare, they developed sprue-like enteropathy from taking olmesartan." (Tina Ho, 558:19-559:14). Finally, on page 82 of the document is a table, first identifying the risk of sprue-like enteropathy, and then stating in the "What is known," column: "**treatment with olmesartan/HCT can lead to severe and chronic diarrhea with substantial weight loss.**" This is a very clear statement recognizing the causality. The third column, "Preventability," which Tina Ho agreed means: "how do you prevent this side effect from occurring when your – from taking the drug, right, how do you prevent it, right?" The box states the condition is preventable, "by identification of patients at risk and by considering discontinuation of

olmesartan/HCT," and Tina Ho confirmed this information was, "based on the best knowledge that we have." (Tina Ho, 559:15-562:21). Again, recognition that the condition is preventable by discontinuing the drug is a strong statement of causation, and fully consistent with the prevailing medical understanding of the condition.

V. CONCLUSION

In conclusion, there is substantial evidence that, taken on aggregate, establishes the causal relationship between olmesartan and sprue-like enteropathy, to a reasonable degree of medical certainty. The literature began with case series that were followed by numerous case reports worldwide, showing marked improvement of enteropathy upon withdrawal of the drug. This was followed by a population-based cohort study that established a cumulative risk gradient and specificity to olmesartan. The finding of a biologically plausible mechanism provided additional evidence for causality. The significant series of adverse event reports demonstrating patients suffering with the clinical syndrome that characterizes olmesartan enteropathy, and documenting a large number of cases with positive dechallenges and rechallenges, is further important evidence establishing and corroborating the causal relationship. In a commentary on the above-cited French cohort study (Basson M, Mezzarobba M, Weill A, Ricordeau P, Allemand H, Alla F and Carbonnel F. Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. Gut. 2016 Oct;65(10):1664-9.), recently published in the prestigious *Annals of Internal Medicine*, Talley NJ. Use of olmesartan for ≥ 1 year was associated with hospitalization for intestinal malabsorption. Ann Intern Med. 2015 Dec 15;163(12): Dr. Nicholas Talley writes:

> The well-conducted database study by Basson and colleagues puts to bed any controversy surrounding the association between the ARB olmesartan and severe intestinal enteropathy pathologically resembling celiac disease… Evidence supporting a causal relation now includes the strength of association, consistent findings, evidence of improvement in most patients after discontinuation, and relapse on drug reintroduction.

I agree with this conclusion that causality has been established. The listing of olmesartan as a cause of villous atrophy and sprue-like enteropathy is a non-controversial assertion in the medical literature, and confirms the scientific consensus that causality has been established.

Very truly yours,

Benjamin Lebwohl, M.D.

November 30, 2016

Exhibit 1

Date of preparation: November 27, 2016

Benjamin Lebwohl, MD, MS
218 Soundview Avenue
White Plains, NY 10606
917-302-2001
BL114@cumc.columbia.edu

Place of Birth: New York, NY
Citizenship: USA

ACADEMIC APPOINTMENTS, HOSPITAL APPOINTMENTS, AND OTHER WORK EXPERIENCE

Academic Appointments

07/2013 - present	**Columbia University College of Physicians & Surgeons** Assistant Professor of Medicine and Epidemiology	New York, NY
09/2011 – 06/2013	**Columbia University College of Physicians & Surgeons** Assistant Professor of Clinical Medicine and Epidemiology	New York, NY
07/2011 – 08/2011	**Columbia University College of Physicians & Surgeons** Assistant Professor of Clinical Medicine	New York, NY
07/2010 – 06/2011	**Columbia University College of Physicians & Surgeons** Instructor in Clinical Medicine	New York, NY

Hospital Appointments

07/2010 - present	**New York-Presbyterian/Columbia University Medical Center** Assistant Attending	New York, NY

EDUCATION

07/2008 – 06/2010	**Columbia University, Mailman School of Public Health** MS in Biostatistics, June 2010	New York, NY
08/1999 – 05/2003	**Columbia University, College of Physicians & Surgeons** MD, May 1999	New York, NY
09/1995 – 06/1999	**Harvard College** AB in Music, June 1999	Cambridge, MA

TRAINING

07/2007 – 6/2010	**Division of Digestive and Liver Diseases, Department of Medicine, NewYork Presbyterian Hospital/Columbia** Gastroenterology Fellow	New York, NY
06/2006 – 05/2007	**Department of Medicine, NewYork Presbyterian Hospital/Columbia** Chief Medical Resident	New York, NY
06/2003 – 06/2006	**Department of Medicine, NewYork Presbyterian Hospital/Columbia** Medicine Resident	New York, NY

LICENSURE AND BOARD CERTIFICATION

New York State license #233671
ABIM certified for internal medicine 2006 through 2016
ABIM certified for gastroenterology 2010 through 2020

HONORS AND AWARDS

Awards

2015-2018: Ewig Clinical Scholar Award, in recognition of clinical teaching.

2014-2017: Lewis V. Gerstner, Jr. Scholar, Columbia University. Awarded to four young physician-scientists at the College of Physicians and Surgeons at Columbia University to conduct translational research.

2013-2016: Irving Scholar Award. Approximately 4 awardees annually, open to applicants from all clinical departments at the College of Physicians and Surgeons at Columbia University Medical Center.

2013: American Gastroenterology Association/Gastroenterology Research Group Young Investigator Award in Clinical Science. (One annual awardee)

2010: Recipient, Clinical Reviewer Award, Gastrointestinal Endoscopy.

2008: Physician of the Year Award, fellow category, presented by the Department of Nursing at NewYork Presbyterian Hospital.

2004: Inductee, Arnold P. Gold Foundation Circle of Excellence, elected by third-year medical students.

2004: Winner for intern class, Department of Medicine House Staff Award, in recognition of excellence in clinical

teaching at NewYork Presbyterian Hospital. (One annual awardee)

2003: Inductee, Alpha Omega Alpha.

1999: Joseph Garrison Parker Prize, awarded to a student who intends the profession of medicine and who has an unusual breadth of interests outside the specifically premedical curriculum. (One annual awardee)

1999: Inductee, Phi Beta Kappa.

Invited Lectureships

2016: Gastroenterology Grand Rounds, Weill Cornell Medical Center: "What's Going On with Gluten?"

2016: Gastroenterology Grand Rounds, SUNY Downstate Medical Center: "Update on Celiac Disease and Gluten Sensitivity"

2016: Pediatric Gastroenterology Grand Rounds, Columbia University: "Update on Celiac Disease and Gluten Sensitivity"

2016: American Gastroenterological Association Regional Practice Skills Workshop, New York. "Academic Practice"

2016: Gastroenterology Grand Rounds, Lennox Hill Hospital, New York: "What's Going On with Gluten?"

2015: American Society of Nutrition, Advances and Controversies in Clinical Nutrition, Long Beach, CA. "Gluten Sensitivity: New Epidemic or Current Craze?"

2015: Lecturer and Dissertation Opponent: University of Umeå, Sweden. "The Multifactorial Etiology of Celiac Disease"

2015: Division of General Medicine Grand Rounds, Columbia University. "Update on Colorectal Cancer Screening and Colonoscopy Quality."

2015: Session Chair and Speaker, International Celiac Disease Symposium, Prague, Czech Republic. "Mechanisms and possible modulation of refractory celiac disease"

2015: Digestive Disease Week, Washington, DC. "Suspected Celiac Disease: How to Secure a Diagnosis?"

2015: Department of Medicine Grand Rounds, Columbia University; John Loeb Lecture. "Celiac Disease: Causes and Consequences"

2015: Peter D. Stevens Course on Innovations in Digestive Care, New York. "Diagnosis and Treatment of Celiac Disease"

2015: Food and Drug Administration Conference: Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics, Washington, DC. "Role of Histology to Measure Clinical Benefit and Appropriate Timing of Assessment"

2014: New York Society for Gastrointestinal Endoscopy Annual Course, New York. "Update on Diagnosis and Managing Celiac Disease."

2014: Digestive Disease Week, Chicago, IL. "Screening and Diagnosing Celiac Disease: What Are the Benefits?"

2014: Gastroenterology Grand Rounds, Lennox Hill Hospital, New York: "Update on Celiac Disease and Gluten Sensitivity"

2014: Pediatric Gastroenterology Grand Rounds, Weill Cornell Medical Center, New York: "Update on Celiac Disease and Gluten Sensitivity"

2013: Gastroenterology Grand Rounds, Weill Cornell Medical Center, New York: "Studying Celiac Disease with Large Data Sets"

2013: Gastroenterology Grand Rounds, NYU Langone Medical Center: "Studying Celiac Disease with Large Data Sets"

2013: International Celiac Disease Symposium, Chicago, IL. "Correct Diagnostic Approach"

2013: International Celiac Disease Symposium, Chicago, IL. "What Happens When Your Diet is Less Than Scrupulous"

2013: Research Forum Co-chair, Digestive Disease Week, Orlando, FL. "Advances in Celiac Disease Diagnosis"

2013: Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm Sweden: "Decreased Risk of Celiac Disease in Patients with Helicobacter pylori Colonization"

2012: Research Forum Co-chair, Digestive Disease Week, San Diego, CA. "Celiac Disease: Neither Rare Nor Trivial"

2012: Gastroenterology Grand Rounds, Mount Sinai Hospital, New York: "Studying Celiac Disease with Large Data Sets"

2012, 2015: Keynote Address, Columbia University Department of Medicine Intern Retreat

2012: Career Forum Panelist: Careers in Epidemiology. Mailman School of Public Health, Columbia University.

2011: Clinical Epidemiology Unit, Karolinska Institute, Stockholm Sweden. "Adherence to Biopsy Guidelines Increases Celiac Disease Diagnosis"

ACADEMIC SERVICE

2015-present: Gastroenterology Fellowship Clinical Competence Committee
2015-present: Gastroenterology Fellowship Evaluation Committee

- These two committees meet quarterly for the purpose of monitoring the performance of each gastroenterology fellow and to develop structural changes to the fellowship program in response to fellow feedback.

2014-present: Society of Practitioners Executive Council

- The Society of Practitioners is an association of practicing faculty, both full-time and voluntary, at Columbia University who are dedicated to the betterment of both patient care and professional activities at our medical center. This group is independent of both the University and the Hospital. The Executive Council meets monthly with the hospital leadership to discuss issues related to patient care of mutual concern to physicians and administration.

2014-2015: Epidemiology General Exam Committee

- We developed and graded the general (written) exam for PhD candidates in Epidemiology at the Mailman School of Public Health.

2013-present: Digestive Disease Week Abstract Review Committee

- I serve on a four-person committee of the American Gastroenterological Association that evaluates all abstracts related to celiac disease submitted to this annual national meeting.

2013-present: Tripartite Request Assessment Committee (TRAC)

- This committee, consisting of representatives from Columbia University Medical Center, Weill Cornell Medical Center, and NewYork Presbyterian Hospital, evaluates all requests for clinical data for the purposes of quality improvement or research projects. The committee meets weekly by teleconference.

2011-present: ColumbiaDoctors Quality Committee

- This committee meets monthly to develop policies and procedures for the faculty practice of Columbia University Medical Center, with an emphasis on implementation of the electronic medical record and monitoring adherence to federally mandated reporting measures.

2011-present: Academic Advisor, Mailman School of Public Health

- I would meet twice yearly (and more often as needed) with masters degree candidates, providing advice on course selection, courseload, and career plans for the following students:
    - Wai Sha (Sally) Cheung, '14
    - Ravi Pasam, '14
    - Katherine Infante, '15
    - Mirko Savone, '16
    - Richa Gupta, '16
    - Aster Meche, '17
    - Matthew Cato, '17
    - Francesco DeMayo, '17

2011-present: Thesis Reader in Epidemiology

- I read drafts and graded the final masters thesis for the following students at the Mailman School of Public Health:
    - Tim Wen: 2011-2012
    - Stephen Mooney: 2011-2012
    - Miriam Gofine: 2014-2015

- Kirsten Quiles: 2014-2015
- Kevin Yao: 2015-2016
- Trang Tran: 2015-2016

2010-present Medicine House Staff Recruiting Committee
2010-present: Gastroenterology Fellowship Recruiting Committee

- My participation in the above two committees consists of interviewing candidates for these programs and attendance of ranking sessions.

PROFESSIONAL ORGANIZATIONS AND SOCIETIES

MEMBERSHIPS AND POSITIONS

2016-present: member, Research Policy Committee, American Gastroenterological Association

2015-present: member, Research Advocacy Subcommittee, Government Affairs Committee, American Gastroenterological Association

2013-2015: Treasurer, North American Society for the Study of Celiac Disease

2011-present: member, North American Society for the Study of Celiac Disease

2011-2015: member, Intestinal Disorders Committee, American Gastroenterological Association

2010-present: member, Herbert Irving Comprehensive Cancer Institute

2008-present: member, American Society for Gastrointestinal Endoscopy

2009-present: member, American College of Gastroenterology

2006-present: member, American Gastroenterological Association

CONSULTATIVE

2015-2016: New York City Department of Health and Mental Hygiene, Colon Cancer Continuous Quality Improvement Toolkit

2015-present: American Association of Medical Colleges: Public Health in Medical Education Task Force

2014-present: Medical Advisory Board, Executive Health Examinations

2014-present: Scientific Advisory Board, National Foundation for Celiac Awareness

JOURNAL REVIEWER

New England Journal of Medicine
JAMA

Gastroenterology
Gut
Clinical Gastroenterology and Hepatology
Digestive Diseases and Sciences
Gastrointestinal Endoscopy
Alimentary Pharmacology and Therapeutics
Journal of Clinical Gastroenterology
Clinical Biochemistry
American Journal of Gastroenterology

EDITORIAL BOARDS

2016-present: Clinical and Translational Gastroenterology
2013-present: Digestive Diseases and Sciences

FELLOWSHIP AND GRANT SUPPORT

- **PRESENT SUPPORT**

AGA Research Scholar Award 7/1/2014-6/30/2017
$270,000
Risk Factors for Celiac Disease and the Health Effects of Gluten
This set of studies involves analyses of the Harvard cohorts so as to determine environmental risk factors for celiac disease, and the development of a gluten index with the aim of determining whether gluten exposure is associated with cardiovascular outcomes.

Louis V. Gerstner, Jr. Scholar 7/1/2014-6/30/2017
$225,000
Gluten and the Microbiome in Individuals With Celiac Disease and Non-Celiac Gluten Sensitivity
This study investigates the microbiome as it relates to the symptomatic effects of gluten. We will conduct a 14-day gluten challenge in patients with celiac disease and in a separate group with non-celiac gluten sensitivity and measure gut microbial composition during this exposure. We will determine whether the severity of gastrointestinal and extraintestinal symptoms experienced during gluten exposure is correlated with reduced species diversity.

- **PAST SUPPORT**

Irving Scholar Award 7/1/2013-6/30/2016
UL1 TR000040
$180,000
The "Celiac Stomach": Gastric Environment and the Risk of Celiac Disease
This set of studies aims to determine whether the risk of celiac disease is affected by exposures to the gastric mucosa, including *Helicobacter pylori* colonization and acid suppression medication.

Alvine Pharma (site PI) 8/1/2013-12/1/2014
$228,894
Evaluation of the Efficacy and Safety of ALV003 in Symptomatic in Celiac Disease Patients
Phase IIB randomized trial of an endopeptidate/endoprotease agent for patients with celiac disease and persistent symptoms with histologic abnormalities.

Alvine Pharma (site PI) 1/1/2013-12/31/2013
$51,876
Evaluation of Patient Reported Outcome Instruments in Celiac Disease Patients
Validation study measuring the sensitivity of patient reported outcome instruments to detect change over time in celiac disease symptoms with and without a gluten challenge.

National Center for Advancing Translational Sciences/National Institutes of Health 7/1/2011-6/30/2013
KL2 RR024157
$200,000
Quality Issues in the Diagnosis of Celiac Disease
Mentors: Alfred I. Neugut and Peter Green
This study aims to identify the underlying causes of the low rates of diagnosis of celiac disease in the United States. The goal of this mentored career development award is to facilitate junior faculty members to achieve research independence.

National Cancer Institute training grant (PI: Alfred I. Neugut) 7/1/2008-6/30/2010
T32-CA095929
Mentor: Alfred I. Neugut
Colorectal Cancer Prevention
As a fellow on this training grant I studied risk factors for suboptimal bowel preparation on colonoscopy using observational data sets.

Celiac Sprue Association (Benjamin Lebwohl) 7/1/2011-6/30/2012
$5,000
Serial Biopsies and Mortality in Celiac Disease: a Population-Based Study
The grant supplements the travel expenses associated with my ongoing collaboration with the Clinical Epidemiology Unit at the Karolinska Institute in Stockholm, Sweden

American Scandinavian Foundation (Benjamin Lebwohl): 5/1/2011-8/31/2011
$5,000
Serial Biopsies and Mortality in Celiac Disease: a Population-Based Study
The objective of this study is to determine whether the results of the "control biopsy," performed 1-3 years following the initial diagnosis of celiac disease, is associated with the mortality rate, which is overall increased in celiac disease. This study utilizes a population-based database of all patients in Sweden with celiac disease spanning the years 1969-2008.

EDUCATIONAL CONTRIBUTIONS

Direct Teaching/Precepting/Supervising

2010-present: General Medicine Inpatient Service

- For a 4-week period every year I serve as attending physician on this service (consisting of 2 interns, 2 residents, and 2 attendings including myself) which cares for inpatients with a variety of general medical illnesses. Rounds, which combine teaching and direct patient care, are performed daily for 2-3 hours.

2010-present: Gastroenterology consultation service

- For 1-2 2-week periods every year I serve as the attending physician on this service (consisting of 2-3 GI fellows and 1-2 medical students or residents) which cares for inpatients in need of gastroenterology consultation. Until 2015 this service included the supervision of endoscopic procedures on consulted patients.

2010-present: Gastroenterology clinic

- For 3-5 4-hour sessions every year I serve as the attending in this outpatient clinic in which GI fellows care for patients with a variety of gastrointestinal illnesses.

2011-present: Lecturer and Small Group Leader, The Body in Health and Disease (M6107)

- I give a 1 hour lecture annually to second-year medical students on the topic of diarrhea covering epidemiology, pathophysiology, differential diagnosis, and treatment. I also precept the students in 2-4 sessions during a 2 week period annually, reviewing case-based questions.

2015: Epidemiology 1

- I was a guest lecturer on the topic of screening for this introductory course for masters students in public health.

2012-present: Section teacher, Clinical Reasoning and Decision Analysis course

- Twice a year I lead medical students in 2 90-minute sessions consisting of case-based discussions in the areas of cognitive bias and decision analysis.

Development of instructional material and curriculum used locally

2015-present: Public Health Thread

- I was appointed the director of this curricular initiative with the objective of incorporating public health into the four years of the medical school curriculum. This includes preclinical lectures on the topics of public health in clinical practice, the development of case-based clinical discussions on topics relating to public health that are relevant to medical students and residents, and the development of a public-health-oriented patient write-up assignment during the medicine rotation in the Major Clinical Year. I delivered a one-hour lecture titled, "What is Public Health?" in March 2016 to the medical students as part of the Mechanisms and Practice component of their Major Clinical Year.

2012-present: Co-Director, Postgraduate Course: Update in Gastroenterology, Hepatology, & Nutrition

- I develop the program for this annual 2-day course that is jointly taught by faculty of Columbia University Medical Center and Weill Cornell Medical Center. Targeted toward a nationwide audience of gastroenterologists, internists, medical oncologists, nutritionists and surgeons, the course focuses on important recent developments and current controversies in gastrointestinal and liver disease. Attendance ranges from 100-200 participants annually.

List of Mentees

2015-present: Jude Fleming: Resident in internal medicine at NewYork Presbyterian Hospital/Columbia. Project: the impact of the gluten-free diet on lamina propria eosinophil concentration among patients with newly-diagnosed celiac disease.

2015-present: Anna Krigel: Resident in internal medicine at NewYork Presbyterian Hospital/Columbia. Project: ethnic variation in celiac disease prevalence in the United States.

2015-present: Monika Laszkowska: Resident in internal medicine at NewYork Presbyterian Hospital/Columbia. Project: the impact of case start time delays on adenoma detection rates among patients undergoing screening colonoscopy.

2015-present: Rajani Sharma: Resident in internal medicine at NewYork Presbyterian Hospital/Columbia. Project: adherence to national guidelines for proton pump inhibitor prescription in patients receiving combination aspirin and anticoagulation.

2015-present: Lauren Golden: Fourth-year medical student at Columbia College of Physicians and Surgeons. Scholarly Project: predictors of persistent villous atrophy among patients with celiac disease undergoing follow-up biopsy.

2015-present: Shria Kumar: Resident in internal medicine at NewYork Presbyterian Hospital/Columbia. Project: incidence and predictors of gastrointestinal bleeding among patients admitted to a medical intensive care unit.

2014-present: Abhik Roy: Fellow in gastroenterology at NewYork Presbyterian Hospital/Columbia. Project: evaluation of adherence to surveillance intervals after navigator-facilitated colonoscopy.

2013-2014: Janie Yang: Fourth-year medical student at Columbia College of Physicians and Surgeons. Scholarly project: Cost Effectiveness of Routine Duodenal Biopsy during Endoscopy to Evaluate Esophageal Reflux. Currently a resident in internal medicine at Mount Sinai Hospital.

2013-present: SriHari Mahadev: Resident in internal medicine at NewYork Presbyterian Hospital/Columbia (and currently a fellow in GI at the same institution). Projects: bowel preparation quality and its impact on adenoma detection, dietician use and celiac disease; predictors of persistent villous atrophy in celiac disease.

2013-2015: Ruby Greywoode: Resident in internal medicine at NewYork Presbyterian Hospital/Columbia. Project: the association of olmesartan use with the presence of diarrhea among patients undergoing endoscopic procesures. Currently a GI fellow at Mount Sinai Hospital.

2013-2014: Eric Braunstein: Fourth-year medical student at Columbia College of Physicians and Surgeons. Project: Development of a clinical prediction rule for difficult sedation in patients undergoing endoscopic

procedures. Currently a resident in internal medicine at Mount Sinai Hospital.

2011-2014: Anna Tavakkoli: Resident in internal medicine at NewYork Presbyterian Hospital/Columbia. Project: vitamin D levels and autoimmunity in patients with celiac disease; long-term outcomes in individuals with non-celiac gluten sensitivity. Currently a GI fellow at the University of Michigan.

2011-2015: Max Pitman: Fourth-year medical student at Columbia College of Physicians and Surgeons. Project: predictors of duodenal biopsy among patients undergoing upper gastrointestinal endoscopy. Currently a first-year GI fellow at New York University Langone Medical Center.

2010-2012: David Narotsky: Medical student at Johns Hopkins University School of Medicine. Project: bibliometric analysis of celiac disease publications. Currently a Resident in internal medicine at NewYork Presbyterian Hospital/Columbia.

Educational Administration and Leadership

2015-present: Gastroenterology Fellows Quality Improvement Projects

- In partnership with the fellowship program leadership, I developed a team-based quality improvement program in which teams of 3-4 fellows, under the guidance of a faculty member, collaborate on an annual project related to improving clinical practice, with an emphasis on identification of systems inefficiencies and measurement of outcomes. Teams present their findings at an annual faculty meeting dedicated Quality Improvement. Teams have the option to obtain Institutional Board Review approval so as to publish their findings.

Instructional/Educational Materials used in Print or other Media

2015: "Don't Just Go Gluten-Free; Why You Need to be Tested First"

- I provided the content and led this Webinar that was hosted by the National Foundation for Celiac Awareness.

Community Education

2016: Presentation, Gluten Intolerance Group of Richmond, Virginia

2013: Presentation, Gluten Intolerance Group of Asheville, North Carolina

2014: Presentation, Colin Leslie Walk for Celiac Disease Research

2012, 2015: Presentation, gluten-free family weekend retreat, New Jersey Y Summer Camps.

REPORT OF CLINICAL AND PUBLIC HEALTH ACTIVITIES AND INNOVATIONS

Practice or Public Health Activities

2010-present: Gastroenterology clinical practice

- My clinical practice focuses on celiac disease and other gluten-related disorders, as well as general gastroenterology. I perform office consultation and procedures (upper gastrointestinal endoscopy and colonoscopy) with patient contact totaling 10 hours weekly.

Clinical or Public Health Innovations

2011-present: Screening Colonoscopy Report Cards

- In collaboration with information technology personnel at NewYork Presbyterian Hospital, I developed a system for the measurement of colonoscopy quality indicators including the adenoma detection rate, which is widely regarded as the most important process measure in screening colonoscopy. We distributed report cards to gastroenterology faculty, comparing the recipient's adenoma detection rate to his/her peers, using anonymized suite-wide reporting. To my knowledge we were the first academic medical center in New York City to provide benchmarked feedback to providers regarding their adenoma detection rates. Our method of reporting has been incorporated into the Colonoscopy Quality Improvement Toolkit developed by the New York City Department of Health and Mental Hygiene.

Clinical or Public Health Administration and Leadership

2016-present: Director of Quality Improvement, Division of Digestive and Liver Disease
2015-2016: Co-Director of Quality Improvement, Division of Digestive and Liver Disease

- I review all cases of potential medical errors related to adverse outcomes in the division of gastroenterology, submitting written reports to the Quality and Patient Safety Committee of NewYork Presbyterian Hospital.

Additional Clinical or Public Health Service Activities

2016-present: Co-Chair, Quality Committee, Citywide Colon Cancer Control Coalition (C5) (member since 2010)

- Under the auspices of the New York City Department of Health and Mental Hygiene, this coalition consists of physicians, allied health professionals, and public health officials, with the aim of increasing the rate of screening for colorectal cancer and improving the quality of screening. As a Co-chair of the Quality Committee (which meets in person semiannually and hosts 2-3 additional conference calls per year) I have advised the coalition on the choice of benchmarks and methods of reporting.

PATENTS & INVENTIONS

None

PUBLICATIONS

Original, Peer-Reviewed Publications

1. Blackett JW, Rosenberg R, Mahadev S, Green PH, ***Lebwohl B**. Adenoma Detection is Increased in the Setting of Melanosis Coli. J Clin Gastroenterol. 2016; in press.

2. Ludvigsson JF, **Lebwohl B**, Ekbom A, Kiran R, Green PH, Höijer J, Stephansson O. Outcomes of pregnancies for women undergoing endoscopy while they were pregnant-a nationwide cohort study. Gastroenterology. 2016; in press.

3. Kumar S, Gress F, Green PH, ***Lebwohl B**. Chronic pancreatitis is a common finding in celiac patients who undergo endoscopic ultrasound. J Clin Gastroenterol. 2016; in press.

4. Roy A, Mehra S, Kelly CP, Tariq S, Pallav K, Dennis M, Peer A, **Lebwohl B**, Green PH, Leffler DA. The association between socioeconomic status and the symptoms at diagnosis of celiac disease: a retrospective cohort study. Therap Adv Gastroenterol 2016;9:495-502.

5. Laszkowska M, Roy A, **Lebwohl B**, Green PH, Sundelin HE, Ludvigsson JF. Nationwide population-based cohort study of celiac disease and risk of Ehlers-Danlos syndrome and joint hypermobility syndrome. Dig Liver Dis. 2016;48:1030-4.

6. Roy A, Laszkowska M, Sundström J, **Lebwohl B**, Green P, Kämpe O, Ludvigsson JF. Prevalence of celiac disease in patients with autoimmune thyroid disease - a meta-analysis. Thyroid. 2016;26:880-90.

7. Kuja-Halkola R, **Lebwohl B**, Halfvarson J, Wijmenga C, Magnusson PK, Ludvigsson JF. Heritability of non-HLA genetics in coeliac disease: a population-based study in 107,000 twins. Gut 2016: in press.

8. Krigel A, Turner KO, Makharia GK, Green PH, Genta RM, ***Lebwohl B**. Ethnic Variations in Duodenal Villous Atrophy Consistent with Celiac Disease in the United States. Clin Gastroenterol Hepatol. 2016;14:1105-11.

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diabetes. J Pediatr. J Pediatr. 2016;169:49-54.

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13. **Lebwohl B**, Luchsinger JA, Freedberg DE, Green PH, Ludvigsson JF. Risk of dementia in patients with celiac disease: a population-based cohort study. J Alzheimers Dis. 2015;49:179-85.

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15. Emilsson L, **Lebwohl B**, Sundström J, Ludvigsson JF. Cardiovascular disease in patients with coeliac disease: A systematic review and meta-analysis. Dig Liver Dis. 2015;47:847-52.

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17. **Lebwohl B**, Green PH, Genta RM. The coeliac stomach: gastritis in patients with coeliac disease. Aliment Pharmacol Ther. 2015;42:180-7.

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23. **Lebwohl B**, Emilsson L, Fröbert O, Einstein AJ, Green PH, Ludvigsson JF. Mucosal healing and the risk of ischemic heart disease or atrial fibrillation in patients with celiac disease; a population-based study. PLoS One 2015;10:e0117529.

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study. Clin Gastroenterol Hepatol 2015;13:1111-1117.

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improve detection of celiac disease in patients with iron deficiency anemia. Am J Gastroenterol 2014;109:769-70.

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INVITED AND/OR PEER-SELECTED PRESENTATIONS AT REGIONAL, NATIONAL OR INTERNATIONAL LEVELS:

See ***Invited Lectureships*** section in **Honors and Awards**

Exhibit 2

In re: Benicar (Olmesartan) Products Liability Litigation

Reliance List for Dr. Benjamin Lebwohl

Deposition Transcripts

Allen Feldman – 5/6/16 Deposition Transcript and Exhibits

Ex. No.	Description	Bates No.
335	Clinical Safety & Pharmacovigilance Org Chart	OLM-DSI 0003484145
336	Pharmacovigilance Org Chart	OLM-DSI 0003484146
337	Curriculum Vitae Allen R. Feldman, M.D.	OLM-DSI 0014378462-64
338	Performance Evaluation 8/12/04	OLM-DSI 0014379830-978
339	FY 14 DSPD Mid-Year Form: Allen Feldman	OLM-DSI 0014379822-25
340	FY 14 DSPD Annual Review Allen Feldman	OLM-DSI 0014379984-89
341	E-mail, 7/30/14 Subject, DS Interview Notes - Allen Feldman	OLM-DSC 0000544809-11
342	E-mail Thread, 3/14/06 Subject, Benicar HCT	OLM-DSI 0011421183-84
343	MedWatch Form	OLM-DSI 0004773536-38-R
344	MedWatch Form	OLM-DSI 0001099317-18-R
345	MedWatch Form	OLM-DSI 0001099361-2-R
346	MedWatch Form	OLM-DSI 0001095941-2-R
347	MedWatch Form	OLM-DSI 0004774183-4-R
348	E-mail Thread 6/18/09 Subject, OLM Cases of Celiac Disease	OLM-DSI 0001306341-42
349	E-mail Thread 6/19/09 Subject, OLM Cases of Celiac Disease	OLM-DSI 0001331270-72
350	E-mail, 2/8/10 Subject, Olmesartan and Celiac Disease	OLM-DSI 001401248
351	E-mail, 11/24/09 Subject, Benicar	OLM-DSI 0001227504
352	E-mail, 11/24/09 Subject, Benicar	OLM-DSI 0012323856
353	E-mail Thread Subject, Benicar	OLM-DSI 0001806703-05
354	E-mail, 1/11/10 Subject, Celiac	OLM-DSI 0001934797
355	E-mail 1/12/10 Subject, Celiac	OLM-DSI 0001829457
356	AER Selection Criteria	OLM-DSI 0001829459-62
357	E-mail Thread, 1/14/12 Subject, Olmesartan Products	OLM-DSI 0002076970-77
358	Original Articles-Alimentary Tract Gluten-Free Diet And Steroid Treatment are Effective Therapy For Most Patients with Collagenous Sprue (Rubio-Tapia)	OLM-DSI 0002078229-37
359	E-mail Thread 6/21/12 Subject, Requested AE Report and Medical Inquiry	OLM-DSI 0003380866-67
360	Adverse Event Form 11/29/10	OLM-DSI 0002231343-46

Ex. No.	Description	Bates No.
361	MedWatch Form	OLM-DSI 0001096152-3-R
362	E-mail Thread 9/6/12 Subject, A Further Reference	OLM-DSI 0002078226-28
363	E-mail Thread 7/5/13 Subject, Olmesartan Label Confidential Communication	OLM-DSI 0002113348-53
364	E-mail Thread 3/31/14 Subject, Enteropathy/CT with ANSM: Minutes	OLM-DSI 0012332415-16
365	E-mail, 10/26/15 Subject, Article - FYI	OLM-DSC 0002923884
366	Immunopathogenesis of Olmesartan-Associated Enteropathy (Marietta)	OLM-DSC 002923885-96
367	E-mail Thread 12/3/15 Subject, Literature Citation from US	OLM-DSI 0012439080-82

Donald Hinman – 5/26/16 Deposition Transcript and Exhibits

Ex. No.	Description	Bates No.
451	Donald J. Hinman curriculum vitae	OLM-DSC-0004041803 - OLM-DSC-0004041804
452	E-mail(s)	OLM-DSC-0000143986 - OLM-DSC-0000143988
453	E-mail(s)	OLM-DSC-0000143996 - OLM-DSC-0000143998
454	E-mail(s)	OLM-DSC-0003533036 - OLM-DSC-0003533042
455	E-mail(s)	OLM-DSC-0000504080 - OLM-DSC-0000504084
456	E-mail(s)	OLM-DSC-0000357715 - OLM-DSC-0000357717
457	E-mail(s)	OLM-DSC-0000504291 - OLM-DSC-0000504294
458	E-mail(s)	OLM-DSC-0000136640 - OLM-DSC-0000136643
459	E-mail(s)	OLM-DSC-0000136639
460	Draft letter from Professor Haller to Mayo Clinic Proceedings	OLM-DSC-0000136644 - OLM-DSC-0000136645
461	"Olmesartan and Intestinal Adverse Effects in the ROADMAP Study," Mayo Clinic Proceedings	

Yasushi Hasebe – 5/31/16 Deposition Transcript and Exhibits

Ex. No.	Description	Bates No.
462	E-mail(s)	OLM-DSC-0000767648

Ex. No.	Description	Bates No.
463	MedWatch report DSU-2008-01458	OLM-DSC-0001402504 - OLM-DSC-0001402505
464	E-mail(s)	OLM-DSC-0000496517 - OLM-DSC-0000496519
465	E-mail(s)	OLM-DSC-0012324237 - OLM-DSC-0012324240
466	E-mail(s)	OLM-DSC-0000136763 - OLM-DSC-0000136766
467	E-mail(s)	OLM-DSC-0000496855 - OLM-DSC-0000496857
468	Pharmaceutical affairs memo	OLM-DSC-0000007941 - OLM-DSC-0000007942
469	Daiichi-Sankyo memo	OLM-DSC-0000221307 - OLM-DSC-0000221308
470	Minutes of Global Pharmacovigilance Committee Meeting	OLM-DSC-0000221228 - OLM-DSC-0000221229
471	E-mail(s)	OLM-DSC-0000050151 - OLM-DSC-0000050154
472	PowerPoint	Bates numbers cut off
473	"Sprue-like enteropathy associated with OLM situation in France" PowerPoint	OLM-DSC-0000003858 - OLM-DSC-0000003864
474	E-mail(s)	OLM-DSC-0001542048 - OLM-DSC-0001542093
475	E-mail(s)	OLM-DSC-0001541926 - OLM-DSC-0001541943
476	Slip sheet	OLM-DSC-0001541944
477	"Comparison of Local Labeling"	

Hideki Tagawa – 7/14/16 Deposition Transcript and Exhibits

Ex. No.	Description	Bates No.
3000	Resume of Hideki Tagawa	OLM-DSC-0007679434 through 0007679435
3001	Document written in Japanese	OLM-DSC-0007679428 through 0007679430
3002	E-mail dated 4/10/14 (in Japanese)	OLM-DSC-0002093849
3003	Case Report, "Olmesartan Associated Sprue-Like Enteropathy and Colon Perforation"	
3004	Medwatch report dated 10/12/15	OLM-DSI-0004770528-R through 0004770530-R
3005	E-mail string, top one dated 10/4/13 (in Japanese)	OLM-DSC-0002088468 through 0002088470

Ex. No.	Description	Bates No.
3006	Medwatch report dated 10/9/15	OLM-DSI-0004762221-R through 0004762222-R
3007	E-mail string dated 1/16/15 (in Japanese)	OLM-DSC-0002624122
3008	Slide deck, Daiichi-Sankyo France-Case discussion [no Bates-3 pages]	OLM-DSC-0002624123
3009	"No tiff included for this record"	
3010	E-mail string, top one dated 10/22/13	OLM-DSC-0001217066 through 000121707
3011	Slide deck, Daiichi-Sankyo (in Japanese)	
3012	"No tiff included for this record."	OLM-DSC-0001217071]
3013	E-mail string, top one dated 6/7/13 (in Japanese)	OLM-DSC-0000924165 through 0000924170
3014	E-mail string, top one dated 4/22/13 (in Japanese)	OLM-DSC-0000097214 through 0000097220
3015	E-mail string, top one dated 6/14/13 (in Japanese)	OLM-DSC-0000097715 through 0000097722
3016	E-mail string, top one dated 2/28/14 (in Japanese)	OLM-DSC-0000217828 through 0000217832
3017	E-mail string, top one dated 10/4/13, with attached Signal Detection Report Olmesartan dated 10/4/13	OLM-DSC-0001685669 through 0001685714
3018	E-mail string, top one dated 6/20/13 (in Japanese)	OLM-DSC-0000113014 through 0000113017
3019	CSPV Meeting Minutes (Draft) dated 6/13/13	OLM-DSI-0002112916 through 0002112920

Jeffrey Warmke – 8/23/16 Deposition Transcript and Exhibits

Ex. No.	Description	Bates No.
3020	Plaintiffs' Notice of Videotaped Deposition Pursuant to Fed. R. Civ. P. 30(b)(6)	
3021	Document Witness Brought to Deposition Entitled "ROADMAP Key Players"	
3022	Document Witness Brought to Deposition Entitled "ROADMAP Timeline"	
3023	Three Excel Spreadsheets with Budget Information for ROADMAP Witness Brought to	
3024	Deposition Curriculum Vitae of 31 Jeffrey W. Warmke, Ph.D.,	OLM-DSI-0017387609 through OLM-DSI-0017387613
3025	4/7/04 ROADMAP Clinical Trial Protocol,	OLM-DSC-0000230929 through OLM-DSC-0000231014

Ex. No.	Description	Bates No.
3026	Plaintiffs' Amended Notice of Videotaped Deposition Pursuant to Fed. R. Civ. P. 30(b)(6)	
3027	Patient Information for Participation in the Clinical Trial: ROADMAP,	OLM-DSI-0005605932 through OLM-DSI-0005605943
3028	ROADMAP Clinical Study Report,	OLM-DSI-0001802066 through OLM-DSI-0001802308
3029	8/26/09 ROADMAP Statistical Analysis Plan,	OLM-DSC-0000365579 through OLM-DSC-0000365649
3030	1/26/10 ROADMAP Statistical Analysis Plan Table of Contents of Tables, Graphs and Listings of the Trial Report,	OLM-DSI-0006344160 through OLM-DSI-0006344244
3031	2011 The New England Journal of Medicine Original Article Titled "Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes" by Haller, et al	
3032	2006 Journal of Hypertension Original Article Titled "Preventing microalbuminuria in patients with diabetes: rationale and design of the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) Study" by Haller, et al	
3033	Supplementary Appendix: ROADMAP Study, Haller et al	
3034	11/09 E-Mail Chain 259 Among Heyrman, Wang, et al,	OLM-DSI-0004565169 through OLM-DSI-0004565175
3035	3/4-3/5/10 E-Mail Chain Among Caspard, Cuprys, et al,	OLM-DSI-0003999681 and OLM-DSI-0003999682
3036	6/11/10 E-Mail from DSI Public Affairs to DaiichiSankyo - Development Division and DaiichiSankyo - Employees Only -Commercial,	OLM-DSI-0003998943 and OLM-DSI-0003998944
3037	6/16/10 "Olmesartan Cardiovascular Safety" White Paper - FDA Regulatory Response,	OLM-DSI-0011644249 through
3038	12/10/09 E-Mail Chain Among Chavanu, Jaffe, et al,	OLM-DSI-0008208021 through OLM-DSI-0008208024
3039	12/14/09 E-Mail from Reimitz to Sugiyama, Bailey, et al,	OLM-DSI-0005145559 through OLM-DSI-0005145561

Ex. No.	Description	Bates No.
3040	Rough Draft of ROADMAP Manuscript,	OLM-DSI-0005145562-R through OLM-DSI-0005145593. 002-R
3041	12/11/09 E-Mail from Heyrman to Wang, et al,	OLM-DSI-0004508313 through
3042	12/14-12/15/09 E-Mail Chain Among Beer, Fukuchi, et al,	OLM-DSC-0007996789
3043	Draft ROADMAP Manuscript,	OLM-DSC-0007996790 through OLM-DSC-0007996822
3044	2/11 E-Mail Chain Among Chavanu, Nwose, et al,	OLM-DSI-0014167502 through OLM-DSI-0014167504
3045	3/10/11 The New England Journal of Medicine Original Article Titled "Delay in the Development of Microalbuminuria in Patients with Type 2 Diabetes" by Haller, et al,	OLM-DSI-0014167505 through OLM-DSI-0014167515
3046	2/16/11 E-Mail Chain Among Feingold, Laeis, et al,	OLM-DSI-0004987643 through OLM-DSI-0004987647
3047	10/13/15 MedWatch Report for Mfr Report#	SP-2006-003369, OLM-DSI-0004767148- R through OLM-DSI-0004767153- R
3048	5/13/16 MedWatch Report for Mfr Report#	DSM-2008-01071, OLM-DSI-0015261736 through OLM-DSI-0015261739
3049	Case Report Form from ROADMAP Study for Patient #1706005,	OLM-DSI-0006340318 through OLM-DSI-0006340505
3050	5/13/16 MedWatch Report for Mfr Report#	P-2006-003153, OLM-DSI-0015261100 through OLM-DSI-0015261106
3051	Data Clarification Form,	OLM-DSI-0013811016 through OLM-DSI-0013811080

Herve Caspard – 4/7/16 Deposition Transcript and Exhibits

Ex. No.	Description	Bates No.
178A	Curriculum Vitae	OLM-DSI-0012353709 - OLM-DSI-0012353712
179A	Notice to Take Videotaped Oral Deposition	
180A	Performance Management form dated from 2-2-2009 to 4-1-2010	OLM-DSI-0001832048 - OLM-DSI-0001832059

Ex. No.	Description	Bates No.
181A	Performance Evaluation from April 1st, 2010 to March 31st, 2011	OLM-DSI-0001825247 - OLM-DSI-0001825257
182A	Guidance for Industry, Good Pharmacovigilance Practices and Pharmacoepidemiological Assessment	
183A	Report sent by Daiichi Sankyo to the Food and Drug Administration on January 14th, 2010	OLM-DSI-0001247409 - OLM-DSI-0001247433
184A	FDA Drug Safety Communication: FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil	
185A	Olmesartan and Celiac Disease, Analysis, the FDA Database of Spontaneous Adverse Events	OLM-DSI-0005439763 - OLM-DSI-0005439766
186A	Email correspondence	OLM-DSI-0006394709
187A	Email correspondence	OLM-DSI-0003802782 - OLM-DSI-0003802783
188A	Email correspondence	OLM-DSI-0001941994 - OLM-DSI-0001941997
189A	Celiac Disease and Olmesartan Medoxomil, Analysis of the Global Safety Database	
190A	Carbonnel | olmesartan-associated enteropathy: Results of a national survey	
191A	Mayo Clinic: Rubio-Tapia | Severe Spruelike Enteropathy Associated With Olmesartan	
192A	Email correspondence	OLM-DSI-0001401248 - OLM-DSI-0001401253
193A	Email correspondence	OLM-DSI-0005411100 - OLM-DSI-0005411102
194A	Email correspondence	OLM-DSI-0003629041 - OLM-DSI-0003629043
195A	Email correspondence	OLM-DSI-0001401451 - OLM-DSI-0001401454
196A	Email correspondence	OLM-DSI-0001398573
197A	Email correspondence	OLM-DSI-0006981165 - OLM-DSI-0006981166
198A	Minutes of Teleconference on Celiac Disease with Olmesartan	OLM-DSI-0001374893
199	Email correspondence	OLM-DSI-0001379730 - OLM-DSI-0001379732
200	MedWatch 3500A	OLM-DSI-0001095738 - OLM-DSI-0001095739
201	MedWatch 3500A	OLM-DSI-0001099545 - OLM-DSI-0001099546

Ex. No.	Description	Bates No.
202	MedWatch 3500A	OLM-DSI-0001095740 - OLM-DSI-0001095741
203	Email correspondence	OLM-DSI-0001836541
204	MedWatch 3500A	OLM-DSI-0001096116 - OLM-DSI-0001096117
205	Email correspondence	OLM-DSI-0001836624 - OLM-DSI-0001836625
206	Email correspondence	OLM-DSI-0003626985
207	Email correspondence	OLM-DSC-0001432942 - OLM-DSC-0001432944
208	MedWatch 3500A	OLM-DSI-0001099841 - OLM-DSI-0001099842
209	MedWatch 3500A	OLM-DSI-0001099303 - OLM-DSI-0001099304
210	MedWatch 3500A	OLM-DSI-0001099279 - OLM-DSI-0001099280
211	MedWatch 3500A	OLM-DSI-0001099297 - OLM-DSI-0001099298
212	MedWatch 3500A	OLM-DSI-0004773775 - OLM-DSI-0004773776
213	Email correspondence	OLM-DSI-0003803550
214	Email correspondence	OLM-DSI-0005402490 - OLM-DSI-0005402491
215	Email correspondence	OLM-DSC-0001432289 - OLM-DSC-0001432290
216	An Analysis of the Daiichi Sankyo Global Safety Database	OLM-DSI-0001836987 - OLM-DSI-0001837000
217	Letter of Nonimmigrant Petition by Daiichi Sankyo re Dr. Herve Caspard	
218	Mini-Sentinel | Modular Program Report	

Crawford Parker – 5/25/16 Deposition Transcript and Exhibits

Ex. No.	Description	Bates No.
405	Resume of Crawford Parker, III	OLM-DSI-0012520026 - OLM-DSI-0012520028
406	2011 Year-End Daiichi Sankyo - My Performance Evaluation Form for Crawford Parker	OLM-DSI-0007126741 - OLM-DSI-0007126759
407	2012 Year-End Daiichi Sankyo Pharma Development - Performance Management Template for Crawford Parker	OLM-DSI-0003802683 - OLM-DSI-0003802685

Ex. No.	Description	Bates No.
408	FY13 DSPD Annual Review: Crawford Parker	OLM-DSI-0003801646 - OLM-DSI-0003801649
409	7/12 E-Mail Chain Among Li, Suzuki, etc.	OLM-DSC-0000143943 - OLM-DSC-0000143946
410	3/05 Document "Guidance for Industry, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment"	
411	Document "Routine Post-marketing Signal Detection for Olmesartan," by Ford Parker, M.D.	OLM-DSI-0005456783 - OLM-DSI-0005456813
412	12/13 Draft "Olmesartan Query Management Draft Team (OQMT), Team Charter Proposal" Power Point	OLM-DSC-0000284359
413	7/13 E-Mail Chain Among Nishiwaki, Feldman, etc.	OLM-DSI-0002079335 - OLM-DSI-0002079340
414	9/28/12 "Olmesartan and Sprue-like Enteropathy" Document	OLM-DSI-0005673972 - OLM-DSI-0005674270
415	2016 Article "Sprue-Like Enteropathy Associated with Olmesartan: A New Kid on the Enteropathy Block" by Hujoel, Rubio-Tapia	
416	2014 Short Report "Five cases of sprue-like enteropathy in patients treated by olmesartan" by Theophile, et al	
417	"1.3.1.1 Summary of Product Characteristics" Document	OLM-DSC-0000162986 - OLM-DSC-0000163008
418	7/3-7/4/13 E-Mail Chain Among Ishida, Wix, etc., with Attachment	OLM-DSC-0000464729 - OLM-DSC-0000464733
419	2011 Original Article "Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes" by Haller, et al	OLM-DSI-0007494901 - OLM-DSI-0007494911
420	5/24/11-5/26/11 E-Mail Chain Among Hoffman, Gormley, etc.	OLM-DSI-0009328198 - OLM-DSI-0009328203
421	2011 Year-End Performance Executive Calibration Summary: CSPV, for Crawford Parker	OLM-DSI-0005456468 - OLM-DSI-0005456470
422	3/11 E-Mail Chain Among Parker, Varas-Lorenzo, etc.	OLM-DSI-0004027980 - OLM-DSI-0004027982
423	3/11 E-Mail Chain Among Wang, Emura, etc.	OLM-DSI-0006070311 - OLM-DSI-0006070315
424	1/17/11 "Olmesartan Post-marketing Requirements, Update on Status" Power Point by Heyrman	OLM-DSI-0004068693
425	"Topic 8 Olmesartan Safety Updates, North America" Power Point	OLM-DSC-0000475513

Ex. No.	Description	Bates No.
426	2/8/10 E-Mail from Dosunmu to Feldman Attaching 11/12/09 "Olmesartan, Olmesartan Hydrochlorothiazide and Celiac Disease" Document	OLM-DSI-0001401248 - OLM-DSI-0001401253
427	2015 Original Article "Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study" by Basson, et al	
428	"Empirica Signal Output" Document	OLM-DSC-0002168966
429	7/12 E-Mail Chain Among Parker, Feldman, etc.	OLM-DSI-0002123913 - OLM-DSI-0002123916
430	2/12/13-2/13/13 E-Mail Chain Among Raval, Parker, etc.	OLM-DSI-0003301840 - OLM-DSI-0003301844
431	"12/17/09 Olmesartan and Celiac Disease, Analysis The FDA Database of Spontaneous Adverse Events,"	OLM-DSI-0005439763 - OLM-DSI-0005439766
432	12/16/09 E-Mail from Caspard to Feldman	OLM-DSI-0006394709
433	1/10 E-Mail Chain Among Caspard, Feldman, etc.	OLM-DSI-0005411100 - OLM-DSI-0005411102
434	5/13 E-Mail Chain Among Smith, Patel, etc.	OLM-DSI-0002106078 - OLM-DSI-0002106082
435	2012 "Severe Spruelike Enteropathy Associated With Olmesartan" Original Article by Rubio-Tapia, et al	
436	2012 E-Mail Chain Among Parker, Murray, etc.	OLM-DSI-0005576187 - OLM-DSI-0005576188
437	2012 E-Mail Chain Among Arunachalam, Nwose, etc.	OLM-DSI-0003380866 - OLM-DSI-0003380867
438	11/29/10 Adverse Event Form with Initial Reporter Being Dr. Joseph Murray	OLM-DSI-0002231343 - OLM-DSI-0002231346
439	12/4/14 MedWatch Form	OLM-DSI-0001096152-R - OLM-DSI-0001096153-R
440	6/8/10 E-Mail Chain Among Caspard, Feldman, etc.	OLM-DSI-0001836624 - OLM-DSI-0001836625
441	2010 "Gluten-Free Diet and Steroid Treatment Are Effective Therapy for Most Patients With Collagenous Sprue" Original Article by Rubio-Tapia, et al	OLM-DSI-0002078229 - OLM-DSI-0002078237
442	6/25/12 E-Mail Chain Among Stellmacher, Parker, etc.	OLM-DSI-0002122957 - OLM-DSI-0002122962
443	6/21-6/22/12 E-Mail Chain Among Nagendran, Nwose, etc.	OLM-DSI-0002385642 - OLM-DSI-0002385649

Ex. No.	Description	Bates No.
444	6/12 E-Mail Chain Among Nishiwaki, Feldman, etc.	OLM-DSI-0009688591 - OLM-DSI-0009688597
445	11/15/12 E-Mail Chain Among Beckman, Parker, etc.	OLM-DSI-0002127195 - OLM-DSI-0002127197
446	2012-2013 E-Mail Chain Among Parker, DSI Meetings, etc.	OLM-DSI-0009638554 - OLM-DSI-0009638559
447	"Update: Olmesartan & Sprue-like Enteropathy" Document by Ford Parker, M.D.	OLM-DSC-0000007891 - OLM-DSC-0000007902
448	2013 "Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma" Article by DeGaetani, et al	
449	Mini-Sentinel Modular Program Report	OLM-DSI-0002112228 - OLM-DSI-0002112271
450	7/3/13 FDA Drug Safety Communication: "FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil"	
451	Donald J. Hinman curriculum vitae	OLM-DSC-0004041803 - OLM-DSC-0004041804
452	E-mail(s)	OLM-DSC-0000143986 - OLM-DSC-0000143988
453	E-mail(s)	OLM-DSC-0000143996 - OLM-DSC-0000143998
454	E-mail(s)	OLM-DSC-0003533036 - OLM-DSC-0003533042
455	E-mail(s)	OLM-DSC-0000504080 - OLM-DSC-0000504084
456	E-mail(s)	OLM-DSC-0000357715 - OLM-DSC-0000357717
457	E-mail(s)	OLM-DSC-0000504291 - OLM-DSC-0000504294
458	E-mail(s)	OLM-DSC-0000136640 - OLM-DSC-0000136643
459	E-mail(s)	OLM-DSC-0000136639
460	Draft letter from Professor Haller to Mayo Clinic Proceedings	OLM-DSC-0000136644 - OLM-DSC-0000136645
461	"Olmesartan and Intestinal Adverse Effects in the ROADMAP Study," Mayo Clinic Proceedings	

Tina Ho (Volume I) – 3/23/16 Deposition Transcript and Exhibits

Ex. No.	Description	Bates No.
80	Curriculum Vitae of Tina Ho, Pharm.D.	

Ex. No.	Description	Bates No.
81	Clinical Safety and Pharmacovigilance Organizational Chart	OLM-DSI-0003484145
82	Pharmacovigilance Organizational Chart	OLM-DSI-0003484146
83	Risk Management Organizational Chart	OLM-DSI-0003481764
84	SPhD-SPRI Performance Evaluation - 2005 for Tina Ho, Pharm.D.	OLM-DSI-0007276272 thru OLM-DSI-0007276287
85	"Outstanding Nomination - Tina Ho, Director, Risk Management" Document	OLM-DSI-0006391227 abd OLM-DSI-0006391228
86	4/21/14 Adverse Event Reporting for Marketed Products Policy	OLM-DSI-0005604784 and OLM-DSI-0005604792
87	Administrative Policy for Adverse Event Reporting for Marketed Products	OLM-DSI-0006970561 thru OLM-DSI-0006970569
88	10/20/10 Administrative Policy for Adverse Event Reporting for Marketed Products	OLM-DSI-0006983837 thru OLM-DSI-0006983844
89	6/25/10 SOP 502 Review Assessment and Reporting of AE from Non Study Sources	OLM-DSI-0005604869 thru OLM-DSI-0005604878
90	SOP 502 Version 2 Receipt, Assessment, and Reporting of Adverse Events from Non-Clinical Study Sources	OLM-DSI-0006506919 thru OLM-DSI-0006506930
91	SOP 502.3 Receipt, Assessment, and Reporting of Adverse Events from Non-Clinical Study Sources	OLM-DSI-0009160396 thru OLM-DSI-0009160407
92	SOP 502/3 Receipt, Assessment, and Reporting of Adverse Events from Non-Clinical Study Sources	OLM-DSI-0009155586 thru OLM-DSI-0009155597
93	SOP 502.3 Receipt, Assessment, and Reporting of Adverse Events from Non-Clinical Study Sources	OLM-DSI-0009162603 thru OLM-DSI-0009162614
94	SOP 502.4 Receipt, Assessment & Reporting of Aes from Non-Study Sources	OLM-DSI-0001599002 thru OLM-DSI-0001599014
95	SOP 502.5 Receipt, Assessment & Reporting of Aes from Non-Study Sources	OLM-DSI-0007277363 thru OLM-DSI-0007277376
96	SOP 502.6 Receipt, Assessment and Reporting of Adverse Events from Non-Study Sources	OLM-DSI-0004862781 thru OLM-DSI-0004862796
97	SOP 502.7 Receipt, Assessment and Reporting of Adverse Events from Non-Study Sources	OLM-DSI-0006556491 thru OLM-DSI-0006556500
98	SOP 502.8 Receipt, Assessment and Reporting of Adverse Events from Non-Study Sources	OLM-DSI-0007100646 thru OLM-DSI-0007100656
99	Seven-Page Document of 21 CFR 314.80	
100	Guidance for Industry, Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines, Draft Guidance	OLM-DSI-0005604235 thru OLM-DSI-0005604284
101	11/1/10 SOP 003, Version 2.0, Operation of Clinical Safety & Pharmacovigilance Unit	OLM-DSI-0001836060 thru OLM-DSI-0001836067

Ex. No.	Description	Bates No.
102	4/15/12 SOP 003, Version 2.0, Operation of Clinical Safety & Pharmacovigilance Unit	OLM-DSI-0002077416 thru OLM-DSI-0002077424
103	4/15/14 SOP 003, Version 3, Operation of Clinical Safety & Pharmacovigilance Unit	OLM-DSI-0002077993 thru OLM-DSI-0002078000
104	1/24/14 SOP 517 Safety Signal Detection from Spontaneous Adverse Events Reports	OLM-DSI-0005604896 thru OLM-DSI-0005604902
105	12/16/09 SOP 503 Examining Safety Data for Marketed Products	OLM-DSI-0005604890 thru OLM-DSI-0005604895
106	Lawyer-Created Document Entitled "SOP 517 - Safety Signal Assessment"	
107	12/16/09 SOP 517 Safety Signal Detection from Spontaneous Adverse Events Reports	OLM-DSI-0005604813 thru OLM-DSI-0005604821
108	8/22/11 SOP 517 Safety Signal Detection from Spontaneous Adverse Events Reports	OLM-DSI-0007100734 thru OLM-DSI-0007100742
109	4/1/07 RM-SOI-009 Postmarketing Signal Detection	OLM-DSI-0001388169 thru OLM-DSI-0001388177
110	4/1/07 RM-SOI-009 Postmarketing Signal Detection (Signed Version)	OLM-DSI-0006387860 thru OLM-DSI-0006387875
111	3/05 "Guidance for Industry, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment"	
112	12/1/08 RM-SOI-009 Signal Detection for Marketed and Investigative Products	OLM-DSI-0005605158 thru OLM-DSI-0005605170
113	6/18/09-6/19/09 E-Mail Chain Among Ho, Feldman, etc.	OLM-DSI-0003629214 and OLM-DSI-0003629215
114	6/18/09 and 6/29/09 E-Mail Chain Among Ho, Dosunmu, etc.	OLM-DSI-0001363021 thru OLM-DSI-0001363023
115	6/18/09 and 6/19/09 E-Mail Chain Among Fukuma, Ho, etc.	OLM-DSI-0001814228 and OLM-DSI-0001814229
116	6/09 and 7/09 E-Mail Chain Among Ho, Dosunmu, etc.	OLM-DSI-0006939361 thru OLM-DSI-0006939364
117	11/23/09 and 11/24/09 E-Mail Chain Among Feldman, Ho, etc.	OLM-DSI-0001290417 and OLM-DSI-0001290418
118	11/24/09 and 11/25/09 E-Mail Chain Among Fukuma, Ho, etc.	OLM-DSI-0001806748 thru OLM-DSI-0001806750
119	11/25/09 E-Mail Chain Among Fukuma, Ho, Feldman	OLM-DSI-0003627093 and OLM-DSI-0003627094
120	2/8/10 E-Mail from Dosunmu to Feldman	OLM-DSI-0001401248
121	11/12/09 "Olmesartan, Olmesartan Hydrochlorothiazide and Celiac Disease"	OLM-DSI-0001401249 thru OLM-DSI-0001401253
122	1/14/10 Letter from Feldman to Stockbridge Enclosing Safety Analysis Report	OLM-DSI-0001247409 thru OLM-DSI-0001247541

Ex. No.	Description	Bates No.
123	Draft 1/13/10 "Celiac Disease and Olmesartan Medoxomil, An Analysis of the Daiichi Sankyo Global Safety Database,"	OLM-DSI-0001829434 thru OLM-DSI-0001829456
124	MedWatch Report SU-2004-002374	OLM-DSI-0001099814 and OLM-DSI-0001099815
125	MedWatch Report DSU-2007-00520	OLM-DSI-0004769891 thru OLM-DSI-0004769892
126	MedWatch Report SU-2006-004503	OLM-DSI-0001099862 and OLM-DSI-0001099863
127	MedWatch Report SU-2005-004130	OLM-DSI-0004773864 and OLM-DSI-0004773865
128	MedWatch Report SU-2005-003579	OLM-DSI-0004773775 and OLM-DSI-0004773776
129	7/19/05 Post Marketing Safety Adverse Event Contact Log and MedWatch Report SU-2005-003790	OLM-DSI-0011876006 and OLM-DSI-0011876014
130	9/21/05 E-Mail from Robinson to Risk Management, Attaching CIOMS Reports	OLM-DSI-0011816015 thru OLM-DSI-0011816036
131	4/1/07 RM-SOI-007 Global Quality Control of MedDRA Term Selection	OLM-DSI-0005605119 thru OLM-DSI-0005605133
132	4/1/07 RM-SOI-006 MedDRA Coding Guideline	OLM-DSI-0005605171 thru OLM-DSI-0005605198
133	2/25/14 E-Mail Chain Among Nishiwaki, Kaku, Ho, etc.	OLM-DSI-0000098242 thru OLM-DSI-0000098249
134	4/29/14 Memo from Parker, Stellmacher, Tagawa to DSJ CSPV, DSPD CSPV, DSE CSPV	OLM-DSI-0002152495 thru OLM-DSI-0002152497
135	11/8/10 "Analysis of Reactions Related to Diarrhea and Oedema Peripheral for Olmesartan Medoxomil and Its Combinational Products,"	OLM-DSI-0001803871 thru OLM-DSI-0001803877

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Ex. No.	Description	Bates No.
730	Daiichi-Sankyo Performance Management Form Senior Leader 4/1/09-3/31/10	OLM-DSI-0023776682 through 0023776697
731	Risk Management Plan for Olmesartan medoxomil/ Hydrochlorothiazide	OLM-DSI-0002133737 through 0002133818
732	E-mail dated 6/26/12	OLM-DSI-0002123003
733	RM-SOI-015 Clinical Case Processing effective 6/25/10, Version 2.0	OLM-DSI-0005605486 through 0005605507
734	CSPV-SOI-015 Clinical Case Processing effective 3/28/11, Version 2.0	OLM-DSI-0005605199 through 0005605227
735	CSPV-SOI-015 Clinical Case Processing effective 9/18/14, Version 10.0	OLM-DSI-0005605249 through 0005605276

736	Safety Signal Detection for Marketed Products Effective From: 9/1/10	OLM-DSI-0004945245 through 0004945269
737	Safety Signal Detection for Marketed Products Effective From: 4/15/14	OLM-DSI-0004945488 through 0004945510
738	Safety Signal Detection for Marketed Products Effective From: 5/1/16	OLM-DSI-0004945451 through 0004945473
739	CSPV-SOI-025 Legal Case Processing effective 6/4/15, Version 1.0	OLM-DSI-0015239019 through 0015239027
740	CSPV-SOI-025 Legal Case Processing effective 11/19/15, Version 2.0	OLM-DSI-0015238865 through 0015238873
741	E-mail dated 8/4/06	OLM-DSI-0006945094
742	Attachment G, Radar Chart	OLM-DSI-0006945102
743	Daiichi Sankyo Safety Assessment As-Is Report Prepared by Taratec Development Corporation, Issued on 08 September 2006	OLM-DSI-0007878161 through 0007878204
744	Receipt, Assessment, and Reporting of Adverse Events from Non-Study Sources Effective from 4/1/07, Version 1.0	OLM-DSI-0007160734 through 0007160751
745	Receipt, Assessment, and Reporting of Adverse Events from Non-Study Sources Effective From 8/1/08, Version 2.0	OLM-DSI-0004791523 through 0004791533
746	Receipt, Assessment, and Reporting of Adverse Events from Non-Study Sources Effective From 4/1/09, Version 3.0	OLM-DSI-0004945409 through 0004945425
747	Receipt, Assessment, and Reporting of Adverse Events from Non-Study Sources Effective From 1/1/10, Version 4.0	OLM-DSI-0003210944 through 0003210969
748	Receipt, Assessment, and Reportingof Adverse Events from Non-Study Sources Effective From 8/1/10, Version 5.0	OLM-DSI-0005605057 through 0005605081
749	MedWatch report dated 10/10/15	OLM-DSI-0004775145-R through 0004775146-R
750	Receipt, Assessment, and Reporting of Adverse Events from Non-Study Sources Effective From 4/1/07, Version 1.0	OLM-DSI-0004945691 through 0004945708
751	Receipt, Assessment, and Reporting of Adverse Events from Non-Study Sources Effective From 4/1/08, Version 2.0	OLM-DSI-0004945651 through 0004945667
752	Receipt, Assessment, and Reporting of Adverse Events from Non-Study Sources Effective From 4/1/09, Version 3.0	OLM-DSI-0004945634 through 0004945650
753	Receipt, Assessment, and Reporting of Adverse Events from Non-Study Sources Effective From 1/1/10, Version 4.0	OLM-DSI-0004945665 through 0004945690

754	Receipt, Assessment, and Reporting of Adverse Events from Non-Study Sources Effective From 8/1/10, Version 5.0	OLM-DSI-0005605134 through 0005605157
755	Receipt, Assessment, and Reporting of Adverse Events from Non-Study Sources Effective From 4/15/12, Version 6.0	OLM-DSI-0006030971 through 0006030998
756	Receipt, Assessment, and Reporting of Adverse Events from Non-Study Sources Effective From 3/10/14, Version 8.0	OLM-DSI-0004945709 through 0004945736
757	Receipt, Assessment, and Reporting of Adverse Events from Non-Study Sources Effective From 4/15/12, Version 6.0	OLM-DSI-0005605037 through 0005605056
758	E-mail dated 10/31/08	OLM-DSI-0006880033
759	No tiff included for this record	OLM-DSC-0007530295
760	Slide deck, "Causality assessment in Daiichi-Sankyo Group"	
761	Minutes of Global Risk Management Committee Meeting, dated 4/2/09 Final	OLM-DSC-0002475873 through 0002475878

MedWatch Reports

Deposition Exhibits No.	Bates Start No.	Manufacturer Report No
343	OLM-DSI-0004773536	SU-2003-001787
124	OLM-DSI-0001099814	SU-2004-002374
0128; 0212	OLM-DSI-0004773775	SU-2005-003579
0210; 0211	OLM-DSI-0001099279	SU-2005-003760
208	OLM-DSI-0001099841	SU-2005-003790
0130, 0356, 0211	OLM-DSI-0011876015	SU-2005-004027
127	OLM-DSI-0004773864	SU-2005-004130
209	OLM-DSI-0001099303	SU-2005-004130
344	OLM-DSI-0001099317	SU-2006-004486
126	OLM-DSI-0001099862	SU-2006-004503
280	OLM-DSC-0002017070	SU-2006-005001
3050	OLM-DSI-0015261100	SP-2006-003153
0369; 0394	OLM-DSI-0011876187	SU-2006-005527(1)
749	OLM-DSI-0004775145	SP-2006-003299
345	OLM-DSI-0001099361	SU-2006-005596
347	OLM-DSI-0004774183	SU-2007-005968
125	OLM-DSI-0004769891	DSU-2007-00520
346	OLM-DSI-0001095941	DSU-2007-00766
35	OLM-DSI-0001820671	DSU-2008-01458(0)
3048	OLM-DSI-0015261736	DSM-2008-01071
372	OLM-DSC-0002195234	DSM-2009-00672(0)
370	OLM-DSI-0005402816	DSM-2009-00694(0)

Deposition Exhibits No.	Bates Start No.	Manufacturer Report No
229	OLM-DSI-0001096067	DSU-2009-01133
375	OLM-DSI-0001815926	DSU-2009-01133(0)
554	OLM-DSC-0002183749	DSM-2009-00694(2)
379	OLM-DSI-0004802898	DSU-2009-01489(0)
3047	OLM-DSI-0004767148	SP-2006-003369
200	OLM-DSI-0001095738	DSU-2010-00011
201	OLM-DSI-0001099545	DSU-2010-00207
202	OLM-DSI-0001095740	DSU-2010-00485
204	OLM-DSI-0001096116	DSU-2010-01914
0686	OLM-DSI-0015224975	DSU-2010-02503(0)
0360; 0438	OLM-DSI-0002231343	DSU-2010-06561
0361; 0439	OLM-DSI-0001096152	DSU-2010-06561
609	OLM-DSI-0004759443	DSJ-2011-02252
607	OLM-DSI-0004759728	DSJ-2012-11750
604	OLM-DSI-0004759751	DSJ-2012-14868
605	OLM-DSI-0004759801	DSJ-2012-21068
386	OLM-DSI-0001097108	DSJ-2012-21068
3006	OLM-DSI-0004762221	DSU-2013-04684
3004	OLM-DSI-0004770528	SU-2014-100300
463	OLM-DSC-0001402448	DSU-2008-01458
500	OLM-DSI-0003711099	DSU-2009-01026 (0)
	OLM-DSI-0004754590	DSM-2009-00204
	OLM-DSI-0004755871	DSM-2008-00111
	OLM-DSI-0004755884	DSM-2008-00239
	OLM-DSI-0004755891	DSM-2008-00300
	OLM-DSI-0004755968	DSM-2009-00451
	OLM-DSI-0004755970	DSM-2009-00482
	OLM-DSI-0004755985	DSM-2009-00694
	OLM-DSI-0004756038	DSM-2009-01869
	OLM-DSI-0004756139	DSM-2010-01260
	OLM-DSI-0004756141	DSM-2010-01269
	OLM-DSI-0004756222	DSM-2011-00109
	OLM-DSI-0004756250	DSM-2011-00236
	OLM-DSI-0004756325	DSM-2011-00846
	OLM-DSI-0004758839	DSJ-2007-05652
	OLM-DSI-0004759741	DSJ-2012-13566
	OLM-DSI-0004761289	DSU-2012-01841
	OLM-DSI-0004761329	DSU-2012-02939
	OLM-DSI-0004761499	DSU-2012-05283
	OLM-DSI-0004761510	DSU-2012-05368
	OLM-DSI-0004761537	DSU-2012-05969
	OLM-DSI-0004761613	DSU-2012-07932
	OLM-DSI-0004761675	DSU-2012-09190
	OLM-DSI-0004762439	DSU-2008-02107
	OLM-DSI-0004762485	DSU-2009-00162

Deposition Exhibits No.	Bates Start No.	Manufacturer Report No
	OLM-DSI-0004762509	DSU-2009-00531
	OLM-DSI-0004762599	DSU-2009-01026
	OLM-DSI-0004762639	DSU-2009-01282
	OLM-DSI-0004762673	DSU-2009-01835
	OLM-DSI-0004762684	DSU-2009-01963
	OLM-DSI-0004762713	DSU-2009-02204
	OLM-DSI-0004762724	DSU-2009-02266
	OLM-DSI-0004762775	DSU-2010-00207
	OLM-DSI-0004762891	DSU-2010-01718
	OLM-DSI-0004762904	DSU-2010-01914
	OLM-DSI-0004762937	DSU-2010-02706
	OLM-DSI-0004762993	DSU-2010-03745
	OLM-DSI-0004763045	DSU-2010-04766
	OLM-DSI-0004763062	DSU-2010-04862
	OLM-DSI-0004763214	DSU-2011-01068
	OLM-DSI-0004763243	DSU-2011-01739
	OLM-DSI-0004764097	DSM-2008-00607
	OLM-DSI-0004767148	SP-2006-003369
	OLM-DSI-0004769102	DSM-2011-01329
	OLM-DSI-0004769172	DSM-2012-00455
	OLM-DSI-0004769202	DSM-2012-00571
	OLM-DSI-0004769206	DSM-2012-00581
	OLM-DSI-0004769276	DSM-2012-01055
	OLM-DSI-0004769889	DSU-2007-00519
	OLM-DSI-0004772009	DSU-2007-00076
	OLM-DSI-0004772077	DSU-2008-01355
	OLM-DSI-0004772105	DSU-2008-02020
	OLM-DSI-0004772337	DSU-2012-07482
	OLM-DSI-0004772357	DSU-2012-08571
	OLM-DSI-0004772363	DSU-2012-09732
	OLM-DSI-0004773653	SU-2004-002638
	OLM-DSI-0004773852	SU-2005-004027
	OLM-DSI-0004774010	SU-2006-005001
	OLM-DSI-0004774046	SU-2006-005321
	OLM-DSI-0004774074	SU-2006-005527
	OLM-DSI-0004774082	SU-2006-005596
	OLM-DSI-0004774183	SU-2007-005968
	OLM-DSI-0004775145	SP-2006-003299

Documents

OLM-DSI-0003109270 - Exhibit 33 (Diarrhea Report)

Olm-dsi-0003301998 – Exhibit 45 (SLE Report)

OLM-DSI-001401249 – Exhibit 121 (Dosunmu Report)

OLM-DSI-0001247409 – Exhibit 122 (Celiac Report)

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Expert Reports

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- General Report